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POG FEVER AND ACUTE RESPIRATORY

DISTRESS SYNDROMES OF CATTLE

BY

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Thesis submitted for the degree of Ph. D. in the
Faculty of Veterinary Medicine, the University
of Glasgow.

1973.

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GENERAL INTRODUCTION

GENERAL INTRODUCTION

Respiratory disease is very common in cattle and is a cause of great financial loss to the livestock industry in Britain and abroad. The 'calf pneumonia complex', involving viruses, Mycoplasma spp. and certain bacteria, is the main problem in indoor calves. Parasitic bronchitis and pneumonia is the dominant pulmonary disorder in grazing calves and results from infestation with Dictyocaulus viviparus. Although there is still much to be discovered about the aetiology of the 'calf pneumonia complex', most of the disease entities in younger animals have been identified.

In the case of adult cattle, this was not so. Parasitic bronchitis, bacterial and chronic suppurative pneumonia were known to occur in adults and the existence of another disorder, known as fog fever or atypical interstitial pneumonia, was also recognised. Fog fever was a loosely defined condition of adult and young stock which occurred in several epidemiologically distinct situations and which was associated with a variety of pulmonary lesions.

In the first part of this thesis, I have reviewed the literature concerning fog fever in Britain, the U.S.A., Canada and Europe. Fog fever was originally identified as a disease of adult cows grazing fog or foggage, an aftermath pasture, in the autumn (Knowlson 1834 and others). Severe, alarming, respiratory embarrassment, of sudden onset, was a notable clinical sign of fog fever. This name was subsequently misapplied to other respiratory disorders in which acute respiratory distress was the presenting clinical sign so that the term 'fog fever' became almost meaningless. In examining the literature, I have pointed out the times at which the name was wrongly used, and I have distinguished a respiratory syndrome of cattle consistent with fog

fever as understood by earlier workers from the records of other forms of acute respiratory distress. The term 'fog fever' has been widely and wrongly used as a synonym for 'acute respiratory distress with dyspnoea'. I have reserved 'fog fever' to describe the disease in adult cattle at pasture in the autumn: all other diseases in which dyspnoea was the presenting clinical sign have been regarded as 'acute respiratory distress syndromes'.

The second part of the thesis embodies the results of a clinical and pathological investigation of acute respiratory distress syndromes of cattle. This was a combined study to define the pulmonary diseases in terms of their clinical signs, epidemiology and pathology. A large number of animals, of all ages, was examined and all were claimed to be examples of 'fog fever'. In fact, the common feature was the presenting sign of acute respiratory distress, which developed in varied epidemiological circumstances and which was the result of varied pulmonary pathology. The causes of the acute respiratory distress syndrome are defined, largely in pathological terms, in each age and class of stock. The main pulmonary disorders of adult cattle, including fog fever, are also detailed: many of these had not been identified previously.

The third part of the thesis contains the results of the experimental work.

Alveolar epithelial hyperplasia is a severe, diffuse lesion in many cases of fog fever; the proliferating cell type was not known. Before this could be identified, the ultrastructure of the normal bovine lung had to be determined, since there were no satisfactory descriptions in the literature. Histochemistry was also used as an adjunct to the fine structural study. The ultrastructure of the normal bovine lung and of the alveolar epithelium in fog fever is described in the first section.

Michel (1953 and 1954) and Weisman (1970) claimed that fog fever was related to reinfection with D. viviparus: our experimental investigation of this hypothesis involved provocation tests with D. viviparus in recovered cases of fog fever.

Pulmonary disease may be induced in cattle by feeding tryptophan or 3 methyl-indole and several groups of workers have related this to 'acute bovine pulmonary emphysema' in the U.S.A. Further experiments involving tryptophan and 3 methyl-indole in cattle are presented and the relationship of these results to fog fever is discussed.

An attempt to establish baselines for the use of Bordetella pertussis as an adjuvant to reaginic antibody production in cattle produced an acute respiratory distress syndrome with pulmonary pathology comparable to that of fog fever. The possible reasons for this are considered.

MATERIALS AND METHODS

MATERIALS AND METHODS

Experimental animals

- 1) Lungworm-free calves
- 2) Cattle with fog fever

Parasitological techniques

Postmortem techniques

Histological and staining methods

- 1) Fixation
- 2) Staining

Electron microscope techniques

- 1) Fixation
- 2) Embedding
- 3) Staining

Preparation of Micropolyspora faeni antigen and double diffusion test

Ayrshire and Ayrshire cross Friesian bull calves, purchased at 3-5 days of age, were housed individually indoors. They were reared on whole milk until 3-4 weeks old when calf weaner pencils were also introduced (British Oil & Cake Mills Ltd). Milk feeding was stopped at the end of 4 weeks and from then on pelleted ration, hay and water were fed. Regular faecal examination for nematode eggs gave negative results.

2) Cattle with fog fever

A letter was sent to all veterinary surgeons in Scotland in June 1969, 1970, 1971 and 1972. They were asked to notify us of suspected cases of fog fever. Such cases were then purchased from their owners and brought to the Veterinary Hospital, University of Glasgow, as soon as possible. A clinical examination was carried out by a member of the Department of Veterinary Medicine on the farm when time allowed and also at the Veterinary Hospital at the time of admission. Further clinical inspections were made as necessary until slaughter. Animals which died suddenly on farms and which were believed to be cases of fog fever were also brought into the Veterinary Hospital, where a post-mortem was performed. In all instances, follow up visits were made to the farms involved, when other animals were examined, the herd history recorded and further animals purchased as necessary.

Parasitological techniques

Baermann examination of fresh lung was carried out to recover lungworm larvae. The posterior half of one diaphragmatic lobe of the lung was taken and the bronchi fully opened with fine scissors; the exposed lung was then finely chopped with a knife. The minced tissue was placed on a copper filter, 60 mesh gauge aperture, over a Baermann funnel filled with physiological saline at room temperature. The apparatus was kept in a warm room overnight. Next morning, 20-30mls of fluid were run off from the bottom of the funnel and examined in a petri-dish, under a Wild dissecting microscope, for lungworm larvae.

Postmortem techniques

Clinical cases were slaughtered at various times after the onset of illness. Animals were stunned, using a captive bolt pistol, pithed with a light cane, and immediately exsanguinated by jugular section. The organs were examined as soon as possible and selected tissues fixed for electron microscopical and histological examination. In most cases, the specimens examined were freshly killed carcasses, but, occasionally, animals which had been dead for some hours or sets of lungs were received. When the complete animal was available, a full macroscopic inspection of all organ systems was made and tissues removed for further examination as necessary. In all instances, the trachea, bronchi, lungs and broncho-mediastinal lymph nodes were examined. After external inspection and palpation, the trachea and bronchi were opened along their ventral surface with scissors. Two portions of tissue were taken from the bronchial tree and lung at the various levels illustrated in Figure (1) and fixed in separate bottles, one in Carnoy's fluid and the other in corrosive formol. The lung tissue was further examined by multiple incisions into the areas not exposed by bronchial section. Additional samples of tissue were taken from both lungs as required. A minimum number of 40 blocks was fixed from each case.

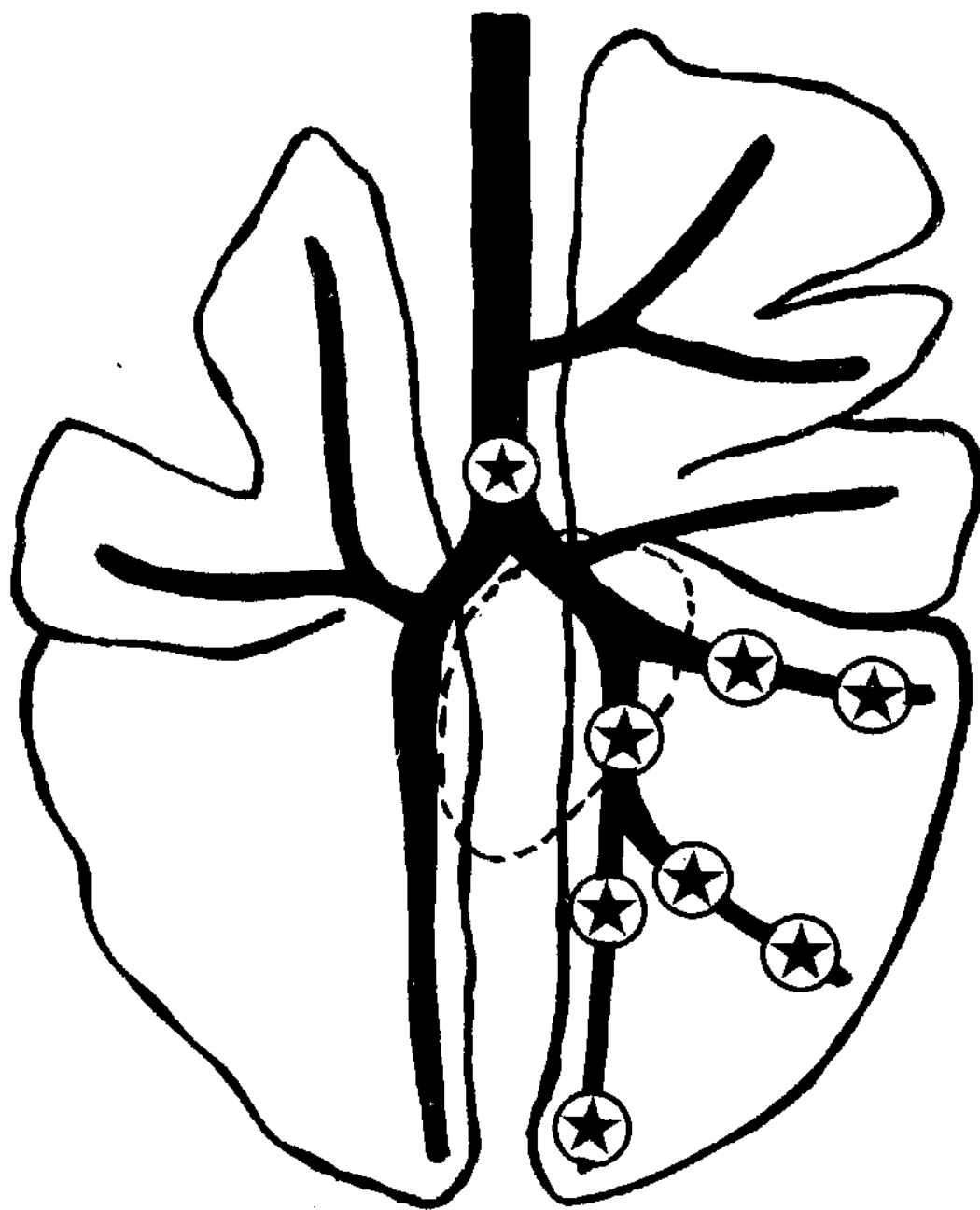


Fig. (1). The standard sites from which samples of the bronchial wall and pulmonary tissues were taken.

Histological procedures

Tissues for microscopical examination were placed in fixative for 24-48 hours. Four fixatives were used and the methods of preparation were as follows:-

a) Carnoy's Fluid (Clayden 1955)

Chloroform	30ml
Absolute alcohol	60ml
and Glacial acetic acid	10ml

b) Corrosive Formol (Carleton and Drury 1957)

Saturated aqueous mercuric chloride	9 parts
40% Formaldehyde	1 part

c) Formol Calcium

Calcium chloride	10gm
Paraformaldehyde	40gm
Water	900ml

A small piece of chalk was added to maintain a neutral pH.

d) Bouin's Fluid

Saturated aqueous picric acid	75ml
40% Formaldehyde	25ml
Glacial acetic acid	5ml

After fixation, tissues were dehydrated and cleared in a double embedding series and finally embedded in paraffin wax under vacuum. Paraffin embedded sections were cut at 6-8 μ thickness on a Cambridge rocker microtome and mounted on glass slides.

Staining procedures

Paraffin sections were routinely stained with haemotoxylin and eosin. When particular morphological changes in the lungs were to be demonstrated more clearly, special stains were used. These were picro-Mallory, van Gieson, Weigert's elastica, alcian blue/P.A.S., Astra blue/Safranin, Toluidine blue, Biebrich Scarlet, Verhoeff-van Gieson, Gordon and Sweet's reticulin stain, periodic acid Schiff, alcian blue, Phosphotungstic acid haemotoxylin, Carbol Chromotrope, Perl's Prussian blue, Rinehart-Abul Haj (Pearse 1968) and Mowry's modification of the Hale Colloidal Iron stain.

Electron microscope methods

Small blocks of tissues 1-2mm in size were excised, as soon as possible after stunning and exsanguination, from the lung and the mucous membrane of the bronchial tree. The specimens were placed in drops of chilled fixative on blocks of dental wax, chopped into pieces 0.5mm in thickness using grease-free razor blades and then transferred to vials containing chilled fixative at 4°C. The small blocks of tissue were left for 1½ hours in 2% or 3% glutaraldehyde at 4°C., rinsed in Sorenson's phosphate buffer and then postfixed for 1 hour in 1% osmium tetroxide. Tissues fixed in paraformaldehyde/glutaraldehyde remained in this fixative for 4-6 hours before being transferred to Michaelis buffer overnight. They were then postfixed in 1% osmium tetroxide for 1 hour. Tissues were also fixed in 1% osmium tetroxide in Millionig's phosphate buffer, for 1½ hours.

Dehydration was through an ascending series of 70%, 90% and absolute alcohol. The tissue blocks were then rinsed with propylene oxide before being embedded in Araldite, Araldite and Epon, or Epon epoxy resin preparations in gelatin capsules. Araldite embedded tissues were left at 57°C. for 48 hours and Araldite/Epon embedded tissues at 80°C. for 36 hours, to allow the resins to polymerise. Epon embedded material was kept at 60°C. for 24 hours to permit polymerisation.

Ultrathin sections were cut on an LKB Mark III ultratome, mounted on copper mesh grids and double stained with saturated uranyl acetate in methanol, then with lead citrate (Reynolds 1963). Stained sections were examined in an AEI electron microscope 6B.

Sections 1-1.5µ in thickness were taken from the same blocks and were mounted on glass slides. They were stained either with azure 11-methylene blue borax (Richardson, Jarrett and Finke 1960) or 1% toluidine blue in 1% borax (Trump, Smuckler and Benditt 1961). These sections were used to locate lesions or orientate specimens for electron microscopical examination.

Fixatives The fixatives were prepared as follows:-

1) Glutaraldehyde

A stock solution of 25% glutaraldehyde stabilised at pH 5-6 was used (TAAB Labs). The fixative was a 2% or 3% solution in 0.067M Sorenson's Phosphate buffer, pH 7.2 - 7.4.

2) Osmium tetroxide (B.D.H., Poole) .

1% Osmic acid was made up in Millonig's buffer at pH 7.2 - 7.4.

3) Paraformaldehyde/glutaraldehyde

A mixture of 1.3% paraformaldehyde and 1.6% glutaraldehyde was prepared in cacodylate buffer at pH 7.2 - 7.4.

The proportions were:-

Paraformaldehyde	2gm
Distilled H ₂ O	25ml
1N NaOH	1-3 drops
25% Glutaraldehyde	10ml
Cacodylate buffer	115ml
Anhydrous calcium chloride	25mgm

Buffers

1) 0.067M Sorenson's buffer was prepared as follows:-

KH_2PO_4 (9.118gm/litre) 1 part
 Na_2HPO_4 (9.512gm/litre) 3 parts
 pH 7.2 - 7.4

2) Millonig's Phosphate buffer was prepared as follows:-

$\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (2.26%) 83ml
 NaOH (2.52%) 17ml
 Distilled H_2O 10ml
 Sucrose 0.54gm
 Final pH 7.2 - 7.4

3) Cacodylate buffer was prepared from a stock 0.1M solution of sodium cacodylate (21.4gm/litre) as a 0.067M solution of 14.331gm/litre. A few drops of concentrated HCL were used to adjust pH to 7.2 - 7.4

4) Michaelis buffer

Sodium veronal 14.7gm
 Sodium acetate 9.7gm
 Distilled water 500ml

Embedding resins Three preparations were used.

1) Araldite Equal parts of Araldite resin (CY212) (CIBA, Cambridge) and Araldite hardener (HY964) (CIBA) were mixed by stirring overnight and stored at +4°C. This formed mixture (1). Before use, 0.6ml of accelerator DY064 (CIBA) and 2.4ml of Di-n-Butyl phthalate (BDH) were added to 57ml of mixture (1) and the whole stirred well for 30 minutes. Hardening was at 57°C. for 48 hours.

2) Araldite/Epon

25ml Epon 812 (Epicote 812) (G.T.Gurr Ltd)
55ml D.D.S.A. (Shell Chemicals)
15ml Araldite resin (CY212) (CIBA)
4ml Di-n-butyl phthalate (BDH)
After thorough stirring the mixture was stored at +4°C.
Before use 1.5% DMP 30 (G.T.Gurr Ltd) was added and well mixed. Hardening at 80°C. continued for 36 hours.

3) Epon

85.4ml Epon 812 (Epicote 812)
86.4ml D.D.S.A.
28.2ml N.M.A. (T.A.A.G.)
The mixture was thoroughly stirred and kept at room temperature. Before use, 2% DMP 30 was added and well mixed. Hardening was at 60°C. for 24 hours.

Section stains were prepared as follows:-

- 1) Uranyl acetate This was a 20% solution of uranyl acetate (M+B, Dagenham) in absolute methanol.

- 2) Lead citrate

Lead nitrate Pb (NO ₃) ₂	1.33gm
Sodium citrate Na ₃ (C ₆ H ₅ O ₇) ₂ H ₂ O	1.76gm
Distilled water .	30ml
1N NaOH	8ml
pH 12.0 - 12.1	

Preparation of Micropolyspora faeni antigen

Strain IMI 134062 of M. faeni, obtained from the Commonwealth Mycological Institute, London, was cultured on either nutrient agar or Czapek Dox agar at 55°C. for 7-10 days. The culture plates were frozen and thawed three times, the liquid drained off, dialysed, filtered through a millipore filter (0.45 microns) and used unconcentrated.

Double diffusion test

Double diffusion was carried out in 1.5% Ionagar No. 2. (Oxoid) prepared with MacIlvain's citric acid buffer (pH 7.2). The pattern used was a central antigen well 4mm. in diameter and five peripheral wells 6mm. in diameter; the distance edge to edge between the central and peripheral wells was 5mm.

At the final reading, made at 5 days, the number and intensity of the lines was noted.

FOG FEVER AND THE ACUTE RESPIRATORY DISTRESS

SYNDROME : A REVIEW OF THE LITERATURE

FOG FEVER OF CATTLE

THE ACUTE RESPIRATORY DISTRESS SYNDROME IN NORTH AMERICA

THE ACUTE RESPIRATORY DISTRESS SYNDROME IN EUROPE

FOG FEVER OF CATTLE : A REVIEW OF THE LITERATURE

Historical aspects

The pathology of the fog fever syndrome

Parasitological findings in fog fever

The aetiology of fog fever

FOG FEVER OF CATTLEHistorical aspects

Discussion of the occurrence of fog fever in Britain is complicated by the lack of a single paper in the literature in which individual cases of the disease are fully documented and the clinical, pathological and epidemiological characteristics are set out. Fog fever was a name originally applied to a respiratory disorder of adult cattle grazing on foggage in the autumn, but the name was subsequently used when similar clinical signs appeared under other epidemiological circumstances, so that the initial specificity became obscured and the term became almost meaningless.

Knowlson (1834) reported a respiratory complaint of cattle, in Yorkshire, known as 'fog fever'. This disease was a rapidly developing respiratory distress condition with dyspnoea which occurred in milk cows at pasture in the autumn and which was liable to have a fatal outcome if the animals were driven any distance. The affected animals were at pasture on grass which had regrown after an earlier cut for hay and the word 'fog' is a traditional 14th century name for such grazings, otherwise known as foggage or aftermath. Cattle were thought to become ill as a result of eating excessive amounts of 'fog'.

Over 100 years later, Barker (1948) described a similar disease in Herefordshire and this was quickly followed by reports from Begg and Whiteford (1948) in Scotland and Leslie (1949) in Yorkshire. These three papers have frequently been used as baselines in the description of pasture or 'classical' fog fever, although the contents of each report is limited clinically, epidemiologically and pathologically. The disease was also recorded by Roberts (1927). Barker (1948) stated that fog fever was a condition giving rise to serious respiratory embarrassment, often fatal, in all breeds of cattle of beef and dairy type during the months from July to November. Affected animals were mainly adults, although young animals in

their first grazing season could become ill. The syndrome developed 10-12 days after a move to aftermath grazings, but in some instances could occur 10 days after a move from aftermath.

Begg and Whiteford (1948) gave the name 'Atypical Interstitial Pulmonary Emphysema' to the respiratory disorder they found in adult milk cows at pasture during September, October and November. This condition was characterised by acute respiratory distress, noticed when the cows were being brought in for the morning milking, but there was no apparent association with any particular type of pasture. MacLean (1948) drew attention to the similarities between fog fever in Wales and this latter syndrome in Scotland. Cates (1948) also commented on the name 'fog fever'.

Leslie (1949) recognised fog fever in the Yorkshire dales as a condition comparable to that described by Begg and Whiteford and also as a disease of adult beef cattle. He noticed an identical seasonal incidence but, again, there was no firm association with actual pasture type.

Although pasture was thought to have a role in the development of the disease, all these accounts are vague and incomplete about grazing history in individual outbreaks. However, the consensus of opinion from these three papers was that fog fever was an acute respiratory syndrome affecting mainly adult cattle at pasture, usually on aftermath grazings, during the autumn. Other conclusions from these papers and various discrepancies are discussed later in relation to the results of this study.

Fog fever was often a dramatic disease in which alarming pulmonary signs could develop very rapidly. When similar degrees of respiratory embarrassment arose during the course of other conditions, the term 'fog fever' was used to describe them. During the 1950's, therefore, 'fog fever' began to be applied more loosely to include other respiratory diseases with dyspnoea, in cattle of any age, under various systems of husbandry. This colloquial use of the name might not have happened had there been a definitive description of the pasture disease or if the aetiology had been

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known. The result was that "fog fever" acquired two meanings during this period, one was in the "classical" sense of a pasture disease and the other was as a synonym for "dyspnoea". Any consideration of fog fever must carefully distinguish between these specific and general meanings.

An important factor in any discussion of fog fever is that the clinical signs, pathological lesions and epidemiology of parasitic bronchitis in cattle were not known at the time the descriptions of "classical fog fever" were written. Parasitic bronchitis was detailed in a series of papers in the 1950's (Jarrett, McIntyre and Urquhart 1953; 1954; 1957 and Jarrett et al 1957), when it became clear that some aspects of what was thought to be "fog fever" could be explained in terms of parasitic disease. Discussion of fog fever must take into account the known pathogenesis and epidemiology of parasitic bronchitis: this is further complicated by the changes in the nature of this disease after vaccination and anthelmintic treatments were introduced in the 1960's. The current epidemiology of lungworm infection in adult animals may not be the same as it was in 1950.

Hudson (1951) wrote of an acute respiratory condition with dyspnoea in Guernsey heifers which had been recently housed. At post-mortem, these animals had "solidification and oedema" of the lungs and a few mature lung worms were present in the trachea. Michel (1953) referred to this as a fog fever syndrome and went on to describe similar responses at different stages of lungworm infection (q.v.). It may be observed that Michel used "fog fever" synonymously with "acute onset dyspnoea" in the clinical sense; this could not have been fog fever, because the animals were not at grass. The acute clinical signs can also be interpreted to be the result of post-patent parasitic bronchitis, as illustrated by Jarrett et al (1957).

Jarrett, McIntyre and Urquhart (1953) subjected cattle with "fog fever" to clinical and pathological examination. The animals, which were

referred to them as typical cases of fog fever by practising veterinary surgeons, were found to have in common severe dyspnoea, expiratory grunt and emphysema. At autopsy, four different types of pulmonary lesion were thought to underlie the severe emphysema, which was responsible for the dyspnoea.

These were :-

- 1) Chronic pneumonia due to Corynebacterium pyogenes
- 2) Parasitic bronchitis
- 3) Cuffing pneumonia
- 4) An apparently distinct entity not associated with any of the former conditions, the lesions of which were reported in more detail by Jarrett (1956).

It was clear from this work that fog fever was used by some veterinary surgeons as a collective term for cases of respiratory distress, often accompanied by emphysema, and that further examination in many instances allowed a more precise diagnosis to be made. Cases of parasitic bronchitis were associated with acute episodes of dyspnoea: the differentiation between such incidents and 'fog fever' appears to have been arbitrary, but may have depended on the absence of adult lungworms in the latter disease (Begg and Whiteford 1948), or upon "the age incidence, the sequence of the sequelae and the temperature curve" (Barker 1948). There is no doubt that 'classical fog fever' and parasitic bronchitis were hopelessly muddled until parasitic bronchitis was defined.

Experimental infection and reinfection of parasite-free calves with Dictyocaulus viviparus was attended by sudden attacks of dyspnoea during the course of the clinical illness. Michel (1954), who conducted these experiments, believed these exacerbations were responsible for many of the cases of fog fever seen by practising veterinary surgeons. This may well have been true, since Jarrett et al (1953) had already shown that parasitic bronchitis could be found at postmortem in some cases. Michel

adopted arbitrary criteria to define fog fever; these were the presence of both dyspnoea and emphysematous crackling. He did not demonstrate that this was an adequate definition to justify comparison with fog fever as characterised by Barker (1948), Begg and Whiteford (1948) and Leslie (1949). Michel used 'fog fever' in the general sense of 'dyspnoea', but this did not mean that the conclusion drawn from that understanding was necessarily applicable to the specific syndrome detailed by Barker.

Michel gave 64 calves an initial infection of lungworms at 70-173 days of age. The actual dose of larvae used was not known, but varied between 5000 and 50,000 larvae. Seven of these calves developed 'fog fever' and died 21 to 26 days after infection. Ten more animals developed the syndrome 47-95 days after this first dose. Seventeen of the remaining animals were reinfected with between 100,000 and 400,000 larvae and 8 of these became dyspnoeic 10-13 days after exposure; the period between first infection and challenge was 106-346 days. Michel stated "no difference was observed between the appearance of fog fever lungs and those of husk infected animals showing the syndrome". He substantiated this claim by an examination of the lungs of 20 cases of fog fever received from veterinary surgeons, but, unfortunately, did not describe the lesions in the lungs of either experimental or field cases examined. Michel produced respiratory signs in some calves by his infection and reinfection experiments; he did not prove that these signs were the result of the same process as 'classical fog fever'. The respiratory conditions described are explicable in terms of the pathogenesis of parasitic bronchitis, although the failure to establish the larval infectivity in control calves complicates the analysis.

The acute respiratory signs during the initial infection could be attributed to :-

- 1) Severe pre-patent husk and the onset of agglaying in early patent husk (days 21-26)
- and 2) Severe patent husk and post-patent husk (days 47 and thereafter).

Two interpretations of the signs after re-challenge are possible. If the first infection ever became established, then re-challenge must have produced the reinfection phenomenon. Since larval infectivity was not controlled, the milder signs seen in the animals which survived to be re-challenged may have been the result of a very low infection, from which the calves gained no immunity; the signs after re-challenge (with 100,000-400,000 larvae) may have been the result of pre-patent husk, therefore. This has also been commented on by Poynter et al (1970).

In all three time periods defined by Michel, Jarrett, McIntyre and Urquhart (1954) and Jarrett et al (1957) stated that severe dyspnoea could develop in husk, but in each case the clinical background and pulmonary lesions were different and characteristic. The pulmonary lesions were not described by Michel.

Michel claimed further support for his implication of lungworms in fog fever by his examination of the lungs of 20 field cases of the disease. He found evidence of lungworm infestation in 15 of the 20 cases submitted. It may be noted that 6 of the cases were examined in December, January, March and April and only one proved negative for lungworms with the tests used. These outbreaks occurred outside the period regarded as typical of the disease by Barker, Begg and Whiteford, and Leslie. These results do not have any significance, since there were no facts to support the initial claim that lungs were from cases of fog fever and not parasitic bronchitis.

Jarrett, McIntyre and Urquhart (1957) investigated the pathogenesis of lungworm infection in cattle and indicated that animals might develop pulmonary lesions similar to those described in fog fever at times when the relationship of these lesions to lungworm infection was not immediately obvious. These were :-

1) In the pre-patent phase - days 17-25

and 2) In the post-patent phase 55-70 days after infection.

In the first instance, careful examination would reveal many small larvae in

the lungs and in the second, worms might be few or absent but examination of history and pathology would help diagnosis.

Although Jarrett, McIntyre and Urquhart (1953) had recognised that fog fever was an apparently separate disease entity, it is probable that many examples of fog fever diagnosed in the field were really cases of husk with dyspnoea that might have been accurately identified with further investigation. However, it was widely accepted that the majority of, if not all, cases of fog fever were connected with lungworms in some way: for example, Downey (1968) introduced a diagnosis of 'fog fever' into an otherwise clear experimental demonstration of post-patent husk in calves, thereby implying that the acute signs were other than those of husk.

Acute respiratory distress had been noticed in cattle at Smithfield Fat Stock show in 1873 and 1952, when there was dense fog or smog at the time of the exhibitions. Several animals died or were slaughtered and the lungs were found to be emphysematous. These outbreaks were recalled by Barber-Lomax (1961). No histological description was published, but pulmonary oedema with hyaline membranes and alveolar epithelial hyperplasia were not features (Loosmore 1972 - personal communication) of the fatal cases. This curious coincidence of acute pulmonary embarrassment and fog, which produced a clinical syndrome apparently similar to fog fever, lead several authors (Jenkins and Pepys 1965; Mackenzie 1966 and Blood and Henderson 1962) to link the two and a "smog-type fog fever" appeared in the literature. This was an unfortunate association since the indoor respiratory complaint was very different epidemiologically from that described by Barker (1948), Begg and Whiteford (1948) and Leslie (1949). Indeed, it has been suggested that this smog-induced illness is a form of heat stroke (Fisher 1963). The fog fever link came about again from the common usage of that term to mean dyspnoea.

Fog fever was generally held to be some consequence of parasitic bronchitis, but, in some situations, clinical signs resembling those

described by Barker (1948) and others, sometimes accompanied by pulmonary lesions comparable to those recorded by Jarrett (1956), were found to occur indoors, where exposure to larvae was unlikely. Sellers (1963) reported an "atypical interstitial pneumonia" of cattle characterised by sudden and violent acute respiratory distress with subcutaneous emphysema. This was found at any time of year and in all ages of animals over 3 months, although particular reference was made to an acute form in 6-12 month old intensively reared beef calves. No indication of the numbers of animals in this study was made. Further reference was made to the syndrome by Omar and Kinch (1966) and Conway (1969), although in my view the outbreaks of atypical interstitial pneumonia described by Conway were the result of parasitic bronchitis.

Jenkins and Pepys (1965) examined sera from cattle with and without respiratory disease. In this survey, 28 animals were diagnosed as suffering from fog fever and twenty of these were found to have detectable precipitating antibodies to farmer's lung hay antigens in their sera and 21 had precipitating antibodies to Micropolyspora faeni, the actinomycete responsible for farmer's lung in man. Jenkins and Pepys compared this serological finding in cattle with those they had made in human subjects with farmer's lung and came to the conclusion that fog fever and farmer's lung were very similar diseases. This interesting observation was repeated in veterinary (Mackenzie 1966, Conway 1969) and medical publications (Crofton and Douglas 1969). Jenkins and Pepys did not define their basis for the diagnosis of fog fever and no pathological description of the cases was published. Only one of the animals in the survey was a case of acute respiratory distress outdoors in the autumn and this animal did not have precipitating antibodies to M. faeni. The cases described by Jenkins and Pepys were not of classical fog fever, since they were indoors: it is not possible to say what lesions these animals had in their lungs or even if the presence of precipitating antibodies was of any significance, since

these antibodies are found in the absence of clinical disease (Pirie et al 1972). There is no evidence to associate farmer's lung of man, a pulmonary disease that follows exposure to mouldy hay, with fog fever in cattle at pasture.

Mackenzie (1966) reviewed much of the literature concerning fog fever and separated the syndrome into several epidemiological forms:-

- 1) A classical picture in late summer and autumn in adult cattle.
- 2) A form involving lung worm infection by D. viviparus or other migrating parasites.
- 3) An indoor type attributed to inhalation of dust and spores.
- 4) A miscellaneous group involving exposure to smog, NO₂, mouldy feedstuffs, kale and certain plants.

The clinical history, pathology and histopathology of classical fog fever was discussed, but the number of animals involved in the study was not mentioned. Mackenzie, again, used fog fever as a synonym for acute respiratory distress with dyspnoea and claimed that "there was a general tendency for considering fog fever-like respiratory disease as a syndrome having more than one aetiology, rather than a single entity".

Fog fever was a name originally given to a disease which seemed to occur in reasonably constant circumstances, although the aetiology was unknown. The term was misapplied and became more confusing as very different epidemiological patterns were added to the original descriptions.

We have defined fog fever (Pirie et al 1971a), in the terms originally used by Barker (1948), Begg and Whiteford (1948) and Leslie (1949), as an acute respiratory distress condition, occurring in adult cattle at pasture in the autumn, with characteristic postmortem findings of interstitial emphysema, pulmonary oedema and hyaline membranes and alveolar epithelial hyperplasia. Using this as a working basis, we have been able to identify the condition in Britain and to refine the definition further. We have also determined that a pulmonary disease very similar to farmer's lung

exists in cattle and that this may be differentiated clinically, pathologically and serologically from classical fog fever (Pirie et al 1971a). The inappropriate use of the term 'fog fever' for cases of acute respiratory disease where the aetiology is not known has also been criticised (Selman et al 1973a). Our view that classical fog fever and farmer's lung are dissimilar diseases is supported by the absence of demonstrable precipitins to M. faeni in the sera of cases of fog fever (Pirie et al 1971b).

Diffuse fibrosing alveolitis of cattle (Pirie and Selman 1972) is a pulmonary disorder with many similarities to "chronic fog fever" described by Mackenzie (1966). There is no evidence to suggest that there is a direct link between diffuse fibrosing alveolitis and fog fever at the moment, although it is possible that the pathogenesis of some of the lesions may be similar. There is no record of an animal exhibiting repeated attacks of fog fever at pasture in the autumn and then being found to have diffuse fibrosing alveolitis.

Roberts et al (1973) have investigated fog fever in Wales and recorded over 800 cases. Only 4 of these were examined pathologically, however, and the report is based on clinical impressions from a number of veterinary surgeons, together with epidemiological details derived from a questionnaire. We have found that veterinary surgeons diagnose fog fever in very different circumstances and that several pulmonary diseases may masquerade as 'fog fever'. It is clear that this disease can only be diagnosed, at present, in terms of the clinical signs, epidemiology and postmortem findings in toto. The syndrome should not be diagnosed on clinical grounds alone. Our survey, like that of Jarrett et al (1953), has emphasised the futility of considering acute dyspnoea with emphysema as a disease in itself. The Welsh survey adds nothing to the literature and serves only to confuse the otherwise growing understanding of respiratory problems in adult cattle.

Fog fever is a colourful, descriptive term which is worth retaining, provided its use is restricted to the original meaning. Fog fever should not be used to describe other respiratory diseases which do not fit the classical picture. 'Atypical interstitial pneumonia' is another phrase used to describe this latter type of disease, but this name itself is contradictory since this type of respiratory disease in cattle is as common as the 'typical' pneumonia, an observation made by Jarrett (1956). The studies of the respiratory disorders of adult cattle are only just beginning and care must be taken with nomenclature to avoid confusion in the future.

The Pathology of the Fog Fever Syndrome

Barker (1948) gave an account of an outbreak of fog fever in adult dairy cattle in which the postmortem lesions were:- interstitial emphysema with bullae; oedema of the lungs and larynx; petechial haemorrhages in the submucosa of the trachea and bronchi. Begg and Whiteford (1948), in a profile of the disease in dairy cows, remarked on the presence of striking emphysema, both interstitial and subcutaneous; bullae of air; congestion and, in some places, pulmonary collapse. Leslie (1949) made the point that young calves remained unaffected, whilst their dams, adult beef cattle, developed pulmonary congestion, oedema and emphysema. None of these authors described histological lesions, but Jarrett et al (1954) recorded alveolar epithelialisation in a case of 'fog fever' submitted for their microscopical examination by Barker. An investigation of pulmonary lesions in fog fever by Jarrett et al (1953) indicated that four types of disease produced common clinical signs:-

- 1) Chronic pneumonia due to C. pyogenes
- 2) Parasitic bronchitis
- 3) Cuffing pneumonia
- 4) An entity, not associated with the previous three, which was characterised by emphysema and pulmonary oedema.

Jarrett (1956) outlined the histological lesions of fog fever as pulmonary oedema, emphysema, alveolar epithelialisation and an absence of septal fibrosis. Jarrett, McIntyre and Urquhart (1957) stated that, with one exception, all material submitted to them as fog fever by practitioners revealed typical lesions of husk, though these lesions were not specified. This exceptional case was presumably the one referred to previously (Jarrett et al 1954) from Barker, when no evidence of parasitic bronchitis was found in the material examined.

Michel (1954) examined 20 lungs from animals believed to have fog fever and stated that the lungs were indistinguishable from those seen in cases of parasitic bronchitis. Parasitological findings in these cases are presented below. Mackenzie (1965 and 1966) provided a

fuller description of cases of fog fever, though, unfortunately, the numbers of animals involved and their histories were not added. The postmortem findings were found to vary with the epidemiology of the syndrome and were considered under 3 main headings -

- 1) classical pasture type in autumn
- 2) indoor disease
- 3) chronic forms

In the classical pasture syndrome, animals might die peracutely with pulmonary oedema, congestion and emphysema. Acute cases died after 24 hours or so of illness, when oedema, hyaline membranes, emphysema and congestion, pulmonary artery hypertrophy, interstitial eosinophilia, alveolar epithelialisation and globule leucocytes were present in the lungs. Centrilobular hepatic necrosis and degenerative change in hypertrophied pulmonary arteries were found in some cases.

Indoor respiratory disease might result from pulmonary lesions similar to those seen in the pasture disease, or from an interstitial pneumonia. This was characterised by fibrosis, asteroid bodies and granulomata, in addition to emphysema, epithelialisation and eosinophils in the trachea, bronchi and lung.

Chronic forms of fog fever were seen especially in housed cattle and the clinical signs of cough, loss of weight and reduced milk yield were insidious in onset, often over several years. In such cases, there was septal infiltration by lymphocytes and plasma cells, thickened alveolar walls, increased reticulin and fibrosis. Centrilobular necrosis of the liver was also found in this syndrome.

Omar and Kinch (1966) described outbreaks of 'Atypical interstitial pneumonia', or 'A.I.P.', in calves 2-6 months of age reared intensively in beef units in East Anglia. Disease generally occurred about the time calves were changing onto a high barley ration and was of sudden onset, with severe respiratory embarrassment and even death within a few hours. Characteristic

lesions of emphysema, oedema, hyaline membranes and epithelialisation were present in the lungs. The aetiology was unknown and seemed unrelated to other longstanding bronchopneumonic lesions present in the same lung. The authors drew attention to the similarity between these lesions and those of pulmonary adenomatosis, fog fever and patent and post-patent parasitic bronchitis. Conway (1969) also reported A.I.P. in Ireland and outlined the clinical and postmortem findings. The cases he described occurred in calves 8-10 months old at grass. All were initially diagnosed as lungworm infections and treated with an unstated drug regime. At post-mortem, emphysema, oedema and alveolar epithelialisation with eosinophil infiltration were present in the lungs and no lungworms were recovered, though the parasitological methods were not given. The diagnosis of A.I.P. was then made and the similarities between these cases and A.I.P. as described by Omar and Kinch were pointed out. Omar and Kinch remarked, in their paper, on the absence of eosinophilia in the lungs of animals examined by them. In view of the inadequate history, pathology and parasitology provided by Conway, it is difficult to attribute his cases to anything other than parasitic bronchitis.

The previous studies to date give a general impression of a clinical syndrome with a wideranging variety of postmortem lesions. None of the studies have provided adequate clinical definition and postmortem correlation, nor have the numbers of animals involved been clearly stated. This is one reason for the development of the concept of multiple aetiology of the fog fever syndrome.

Parasitological Findings in Fog Fever

It must be emphasized at the onset of this discussion that any consideration of this topic is complicated by ignorance of the pathogenesis and epidemiology of parasitic bronchitis at the time when many of the earlier papers on fog fever were written. In particular, further reference must be made to the late pre-patent and the post-patent periods of infection, when the association between parasitic bronchitis and a clinical syndrome with postmortem lesions similar to those ascribed to fog fever might not be apparent without careful clinical and parasitological examination. These considerations were absent in many earlier descriptions of disease and consequently previous diagnoses are now equivocal.

Barker (1948) and Leslie (1949) did not mention that lungworms were present in their cases but implied that they were able to distinguish the fog fever syndrome from parasitic bronchitis in adult cattle. Begg and Whiteford (1948) stated that lungworms were absent in their cases. None of the authors recorded Baermann or bronchial smear examinations, so were only able to exclude obvious adult lungworms in the trachea and major bronchi. Jarrett et al (1954) were unable to find evidence of parasitic bronchitis in at least one instance.

Michel (1954) examined 20 cases of fog fever parasitologically; Table (1) summarises the result. If the diagnosis of fog fever is confined to the months of August-November, then cases 6, 7, 14, 15, 16 must be excluded. Case 13 can probably be placed in the fog fever category. In the 15 cases remaining, 5 had no evidence of the presence of D. viviparus and in 6 of the 10 cases in which D. viviparus was found very small numbers of adults and/or larvae were recovered. One animal, case 10, had sufficient adult worms present to be classed as patent parasitic bronchitis. Michel's study provided no conclusive evidence, either way, of the involvement of D. viviparus in cases of fog fever.

'Fog fever like' signs have been reported on several occasions during natural and experimental infections of cattle with D. viviparus (Michel and

Specimen	Date of Arrival	>1cm long	<1cm long
1	8.10.51	many adults	
2	11.10.51	44	32
3	15.10.51	-	-
4	2.11.51	-	-
5	13.11.51	-	-
6	29.12.51	-	15
7	2. 1.52	38	-
8	13. 9.52	22	6
9	23. 9.52	24	255
10	26. 9.52	1100	660
11	3.10.52	14	-
12	7.10.52	2	2
13	3.12.52	-	-
14	30. 1.53	-	1
15	3. 3.53	2	3
16	18. 4.53	1	-
17	17. 8.53	-	-
18	28. 8.53	-	1
19	1.10.53	-	5
20	6.10.53	-	144

Table (1): the number of immature and mature lungworms Dictyocaulus viviparus recovered from the lungs of 20 cases of fog fever.
(From Michel 1954).

Shand 1955; Michel and Mackenzie 1965; Downey 1968) but these have never been shown to be anything other than the result of the lungworm infection and its known pathology.

Various episodes of respiratory distress or deaths in cattle have been found to be the result of massive infections by aberrant parasites such as Ascaris lumbricoides (Kennedy 1954; Allen 1962; Morrow 1968) and such an experimental infection was made by Taylor (1952). However, there is no known association between classical fog fever at pasture and these singular incidents, which occur from time to time.

The Aetiology of Fog Fever

The aetiology of fog fever is unknown, but many ideas have been put forward to explain the syndrome. The hypotheses involve either possible aetiological agents or the pathogenesis of the disease. In no case has there been adequate experimental proof to support these suggestions.

Knowlson (1834) attributed the syndrome to the ingestion of excess rich foggage and Barker (1948) expanded on this by proposing that protein in such grass produced shock after inducing "sensitisation". Begg and Whiteford (1948) noticed that many immature spiders and their webs were present on the grass and considered the possibility that these might be involved. These latter authors minimised the importance of foggage and claimed to see the disease on all types of pasture, including poor-quality moor-edge grazings.

Michel (1953) suggested that fog fever was a manifestation of parasitic bronchitis in adult cattle and that the syndrome arose at two separate stages, i.e. in the development of a primary lungworm infection and during reinfection: the pathology of husk was not elucidated until several years later.

Jarrett, McIntyre and Urquhart (1957) infected parasite-free calves with either 5000 or 50,000 third-stage larvae of D. viviparus. None of the calves given 50,000 larvae lived longer than 18 days post-infection. At post-mortem at that time, pulmonary oedema and hyaline membranes, emphysema and alveolar epithelialisation were present in many lobules of the lungs. These lesions were comparable to those described in fog fever (Jarrett 1956). However, great numbers of immature worms were present in the trachea and bronchi in a muco-pus exudate and many bronchioles blocked by eosinophil plugs might also be found in areas where collapse of alveoli had taken place. Animals given 5000 larvae exhibited these same lesions to a lesser degree. Extensive alveolar epithelialisation was present in lungs from some animals killed 60-70 days after infection and nematodes were either absent or few in number. Pulmonary oedema and emphysema might also be found.

Animals which have become immune to D. viviparus may show marked pulmonary signs after reinfection, depending on the numbers of viable larvae in the challenge. The lesions underlying this respiratory disorder are associated with the destruction of larvae in small bronchioles and the formation of lympho-reticular nodules at such sites (Jarrett et al 1960, Jarrett and Sharp 1963 and Pirie et al 1971c). Pulmonary oedema and hyaline membranes, severe emphysema and alveolar epithelialisation are not described in this syndrome.

Michel's association of fog fever and parasitic bronchitis may be challenged. Although animals might present with acute respiratory distress in the pre-patent period of parasitic bronchitis, this disease has clinical, epidemiological and pathological differences from fog fever. Cattle re-infected with lungworms have very different pulmonary pathology to that of fog fever though, again, they might exhibit acute pulmonary signs. The post-patent phase of parasitic bronchitis has similar lesions to those described in fog fever and in some instances no lungworms are demonstrable at necropsy. The relationship between post-patent husk and fog fever has not been examined; published descriptions of typical fog fever do not provide enough information for the significance of lungworm infection to be estimated. It has been implied that fog fever and post-patent husk were the same disease (Michel 1953: 1954; Jarrett 1956) but although clinical, pathological and parasitological similarities have been noted, there has been no attempt to investigate any differences between the syndromes. One aim of this study was to define both these conditions and, if possible, distinguish them.

It has been claimed many times that fog fever is an allergy, sensitisation or hypersensitivity to some substance, but these claims remain unsubstantiated (Barker 1948; Beggs and Whiteford 1948; Michel 1953, 1954; Smythe 1954). Hudson (1951) suggested that an allergy to lungworms was associated with the development of fog fever, and instanced a "typical outbreak" in Guernsey cattle. Jarrett, McIntyre and Urquhart (1957) discussed an identical

acute onset respiratory disease attributed to post-patent husk and considered the possibility that alveolar epithelialisation was a reaction to lungworm tissue antigens. Hudson's description was probably of post-patent husk and his suggestion, with that of Jarrett et al, raises fundamental questions about the aetiology of that syndrome but not of fog fever, unless the same mechanism might be responsible for both.

Jenkins and Pepys (1965) attributed some cases of 'fog fever' to an Arthus reaction in the lung and demonstrated precipitating antibodies to M. faeni in the sera of affected animals. Though this was accepted by many workers, Pirie et al (1971b) found that animals with classical fog fever did not have precipitins to M. faeni and that the pulmonary lesions of farmer's lung in cattle were different from those associated with fog fever. Mackenzie (1966) attributed 'indoor fog fever' to possible inhalation of dust and spores. The clinical and pathological descriptions he provided were very like those described in farmer's lung and diffuse fibrosing alveolitis of cattle (Pirie et al 1971a; Wiseman et al 1973; Pirie and Selman 1972), both were very different from the original recordings of fog fever.

The presence of eosinophils in the lungs seems to be one basis for the association of allergy and fog fever. The sudden onset of the disease might also be of significance. Mackenzie (1965) described globule leucocytes in cases of fog fever. These cells are discharged mast cells and are seen in immune responses and parasitic disease (Jarrett, Miller and Murray 1967; Miller, Murray and Jarrett 1967) but their significance in fog fever and their occurrence in other diseases of the bovine lung was unexplored.

Aitken and Sanford (1969a) sensitised cattle to ovalbumen and then challenged them intravenously with the same protein. Pulmonary congestion, oedema and interstitial emphysema were found in some of the lungs at post-mortem, along with hyaline membranes in one animal. These cattle died very quickly after challenge and alveolar epithelial hyperplasia did not develop.

The lung lesions of anaphylaxis were not identical to those of fog fever and alveolar epithelial hyperplasia, an essential part of the pathology of most cases of fog fever, did not occur. Anaphylaxis has not reproduced all the lesions of fog fever and there is no proof that the two conditions are identical.

Hudson (1951) compared the pathology of his cases to that of human asthma and found them very similar. The lesions of status asthmaticus in man have been characterised as :-

"The presence of mucous plugs in the bronchi and bronchioles, the absence of destructive emphysema, occasional areas of bronchiectasis, mucous and serous exudation with eosinophil infiltration of the bronchial tree, occasional granulomatous lesions of the collapsed lung lobules with local eosinophilia" (Dunnill 1971).

The animals described by Hudson did not have lung pathology of this type and the comparison between fog fever and asthma is unsound. Similarities between status asthmaticus and reinfection husk can be found, however.

Lesions remarkably like those of fog fever can also be found in Cadmium fume pneumonitis, a disease which does not appear to have an allergic basis (Crofton and Douglas 1969). The pathology of the fog fever syndrome does not indicate, therefore, an exclusively allergic pathogenesis and the idea of an hypersensitive origin is based mainly on tissue infiltration by eosinophils, cells which are also found in all forms of parasitic bronchitis.

Atypical interstitial pneumonia (Omar and Kinch 1966) is a disease with similar postmortem lesions to fog fever that occurs in animals indoors, where the influence of D. viviparus can be minimised. The aetiology of this syndrome is also unknown. It may be postulated that although A.I.P., post-patent husk and fog fever are different diseases, the same basic mechanism may be responsible for each syndrome.

Fog fever, according to Barker, Begg and Whiteford and Leslie, was a limited clinical syndrome. Lack of knowledge of the cause and course of natural parasitic bronchitis and a relaxation of usage to embrace other forms of acute respiratory distress produced imprecision in the nomenclature. Additional comparisons with other poorly defined conditions in other countries led to the development of the concept of a multiple aetiology syndrome occurring in many different circumstances.

This study was undertaken to define the causes of acute respiratory distress or fog fever and to investigate the pathology of the conditions which were responsible, since there were no satisfactory reports in the literature.

THE ACUTE RESPIRATORY DISTRESS SYNDROME IN NORTH AMERICA:

A REVIEW OF THE LITERATURE

CANADA

UNITED STATES

pasture disease

respiratory disease and mouldy feeds

nitrogen peroxide and pulmonary disease

pulmonary disease and tryptophan administration

Acute onset respiratory distress conditions with interstitial emphysema are seen in North America and are generally referred to under the term 'acute bovine pulmonary emphysema' or 'A.B.P.E.' This disease does have a fairly loose definition (see Griner 1963 below) but not all authors have adhered to this and the name has been given, with the same laxity as fog fever in Britain, to respiratory conditions arising under diverse circumstances. Several conferences at the University of Wyoming were consistent in retaining the name A.B.P.E., but recently 'bovine pulmonary emphysema' (Hyslop 1969) and 'the emphysema-adenomatosis complex' (Dickinson and Piper 1971) have revived the diverse nomenclature. I have attempted to group the American diseases under the heading 'acute respiratory distress syndrome' and to subdivide this wherever possible.

CANADA

Schofield (1924) reported an outbreak of acute pulmonary emphysema in calves and later recorded a similar event in adult cattle at pasture (Schofield 1941). He proposed that this latter condition was connected with the ingestion of rape or kale on certain farms and was the result of the action on the lungs of an enterotoxin, probably produced by Clostridium welchii. Cote (1944) described this clinical syndrome as the respiratory form of rape poisoning. Schofield (1948) enlarged on his previous observations on acute pulmonary emphysema. The typical syndrome developed 3 to 28 days after cattle were moved on to fields of rape or kale and consisted of sudden onset dyspnoea, emphysema and slight jaundice. Additional clinical signs, associated with an alimentary disorder, included constipation or foetid diarrhoea. Necropsy revealed congestion, oedema and emphysema in the lungs, pallor of the liver and kidneys and catarrhal inflammation of the small intestine and abomasum. Microscopical examination confirmed the

presence of rupture and collapse of alveoli in the lungs, pulmonary oedema, cloudy swelling of the parenchyma of the kidneys, centrilobular degeneration and necrosis in the liver and epithelial necrosis in the small intestine. C. welchii was recovered from the alimentary tract of many cases and it was proposed that toxins derived from this organism were damaging the capillary bed of the lung.

Schofield injected toxins, prepared from a broth culture of C. welchii, intra-peritoneally into a cow, night and morning, for 3 days. On the third day, emphysema was recorded, along with an expiratory grunt and an elevated respiratory rate of 80-90 per minute. At postmortem, congestion, oedema and emphysema were found in the lungs. Experimental attempts to produce the pulmonary disorder by feeding cattle housed indoors on rape or turnip tops were unsuccessful.

The syndrome in Canada was associated by Schofield with rape and kale feeding, but he noticed that the disease was also seen when cattle were grazing on second-growth alfalfa, newly seeded pasture or even a weedy field. There is no mention of hyaline membranes or alveolar epithelial hyperplasia in the histological descriptions of these cases, nor is there any proof that all the signs in cattle on different grazings were due to the same cause. The fact that the disease occurred after pasture change is a common link with fog fever, but there is no additional proof of similarity.

O'Donoghue (1960) reviewed Canadian cases and recorded acute pulmonary emphysema in Alberta during summer and autumn. Blood (1962) and Blood and Henderson (1962) gave a full account of acute pulmonary emphysema, but preferred the term "atypical interstitial pneumonia" to those previously used by other authors. Atypical interstitial pneumonia or A.I.P. was seen in an acute or chronic form and all classes of livestock were affected, with the exception of calves less than 3 months of age. Clinical cases might arise in animals at pasture, in feed lots or in barns.

The acute disease was most often found in autumn, seven to twelve days after a pasture change. Clinically, there was a sudden onset of dyspnoea

with an expiratory grunt. Animals might die in 12 hours but usually the 46 course was two to three days. It was said that up to 30% of animals died and many of the rest became chronically affected, unthrifty survivors, in which residual emphysema might be found. Postmortem examination of acute cases revealed the presence of oedema of the larynx and lungs, hyaline membranes and alveolar epithelial hyperplasia accompanying severe interstitial emphysema.

The chronic condition usually became manifest in winter, with a more gradual onset over several days or weeks of tachypnoea, coughing, variable pyrexia, loss of weight and fall in milk yield. Death might ensue weeks or months later, but most animals were disposed of for economic reasons before this time, since clinical recovery was rare. The postmortem lesions in this chronic syndrome were not clearly stated, but the lungs were said to be enlarged and firm, with small flecks of pus in the bronchi. Extensive fibrosis of the lungs with alveolar epithelial hyperplasia and hyaline degeneration of small pulmonary arteries was noted.

Blood regarded the acute and chronic conditions as variations of the same disease, A.I.P., a syndrome he thought virtually identical to 'fog fever'.

The description of the acute form of A.I.P. is very comparable to that of 'classical' fog fever, but the chronic syndrome has more of the characters of bovine extrinsic allergic alveolitis or farmer's lung (Pirie et al 1971a) and fibrosing alveolitis (Pirie and Selman 1972). The clinical and pathological description, though brief, indicates that chronic A.I.P. has much in common with chronic farmer's lung in cattle in Britain (Wiseman et al 1973). In this latter condition, in a dairy herd, tachypnoea, coughing, weight loss and fall in milk yield were found to be the result of pulmonary lesions of farmer's lung. Additional support for this view was provided by Blood himself. He discussed possible aetiologies for the condition and mentioned that the chronic form was worse in animals standing close to the chute down which hay was thrown into the cow-shed. This was the dustiest part and the disease abated when measures were taken to reduce the dust.

Pelletier (1963) and Hyslop (1969) reviewed the literature on acute pulmonary emphysema in Canada and elsewhere, but added no new information or analysis.

UNITED STATES

Maki (1963) presented an exhaustive, uncritical review of all the circumstances in which emphysema had been found in the bovine lung or acute pulmonary signs of unknown aetiology had been noticed, at a symposium on acute bovine pulmonary emphysema, in Laramie. A.B.P.E. has been compared to fog fever by many authors but there has been no sustained, critical attempt to correlate the clinical signs, epidemiology and pathology of the diverse disorders included as the various 'forms' of A.B.P.E. and the term itself has been used inappropriately and misleadingly in a fashion reminiscent of 'fog fever'. This appears to be partly the result of the undue attention given to interstitial emphysema, which cannot be considered to be a disease in itself. Maki (1963) exemplified this by producing an excellent review of interstitial emphysema without relating many of the instances he chronicled to the pasture disease A.B.P.E.

Griner (1963), discussing A.B.P.E., stated "the nomenclature for the disease was variable and the disease was characterised as being acute, non-infectious, occurring in summer or fall, having a sudden-onset and resulting from the transfer of cattle from dry or overgrazed range to an improved pasture".

Maki and Tucker (1963), opening the A.B.P.E. conference, stated "A.B.P.E., as discussed here, is an acute, sometimes chronic, non-contagious, afebrile disease. It is usually characterised by a sudden onset with severe expiratory dyspnoea which is exacerbated by exercise. The disease can occur anytime during the year, but the occurrence is greatest during the summer and fall seasons and is associated with a change in forage. Usually if A.B.P.E. is to occur, it will be manifested within 10 days after cattle have been

transferred from dry summer pasture to an improved green or ungrazed "lush" type of pasture. The morbidity may vary from one to a hundred per cent and the mortality of affected cows might be as high as 50%."

Lung pathology was not included in the definition of the disease but pulmonary oedema, severe interstitial emphysema and some degree of 'pulmonary adenomatosis' were described by Griner (1963) in experimental cattle in which A.B.P.E. had been induced (Tucker and Maki; Maki and Tucker 1962).

A.B.P.E. can be summarised as a sudden onset, dyspnoeic condition occurring in adult beef cattle, mainly in the autumn up to 10 days after a change of grazing. The lung lesions are pulmonary oedema, emphysema and adenomatosis (alveolar epithelial hyperplasia). On this basis, it is clear that A.B.P.E. very closely resembles classical fog fever as it is known in Britain.

If the name A.B.P.E. is restricted to the syndrome specified by Maki and Tucker (1963) it excludes the chronic form of A.I.P. (Blood 1962) and other disorders including pulmonary adenomatosis on mouldy feed, bronchiolitis obliterans, (NO₂) nitrogen peroxide gas poisoning and tryptophan or 3 methyl-indole induced lung disease (v.inf.).

However, A.B.P.E. has been used to embrace four syndromes which may or may not have a similar aetiology:-

- 1) the disease in beef cattle at pasture (see Tucker and Maki 1963)
- 2) a syndrome involving exposure to mouldy feeds, which has also been known as 'pulmonary adenomatosis'
- 3) an experimentally induced lung disorder comparable to 'silo-filler's disease' of man which results from nitrogen peroxide administration
- 4) pulmonary conditions arising after experimental dosage with tryptophan or 3 methyl-indole.

Pasture disease

Maki (1963) credited Butler (1940) and Farquharson and Butler (1944) with the earliest accounts of 'panthers' or 'pulmonary emphysema' in the United States. These reports involved cattle dying of pulmonary emphysema after a move to fresh pasture. Railsback (1945) wrote of an idiopathic pulmonary emphysema, which sometimes achieved epizootic proportions, in Arkansas, when "range is short, the ground dusty and the water supply lacking in either quantity or quality". He suspected this was caused by bacteria and was contagious: some success was claimed for prevention by "mixed bacterin injections" of Corynebacterium or Pasteurella. It has been considered (Maki 1963) that this report records A.B.P.E., but there is no history of move to fresh pasture and the clinical history and pathology are incomplete. Clinical signs included pharyngeal pain and acute onset dyspnoea; pulmonary emphysema was observed at postmortem but pulmonary oedema was not mentioned.

Fox and Roberts (1949) described 37 cases of A.B.P.E. seen from 1942-1949. Characteristic signs were sudden onset dyspnoea, expiratory grunt and accelerated respiratory rate with subcutaneous emphysema. Full clinical history was not provided.

Additional reports of pasture linked illness were given by Lindley (1950), Wictor (1952), Moore (1952), Goodman (1956), Klussendorf (1954) and Gibbons (1956; 1962) but little was added to previous knowledge other than a variety of new names.

A conference on A.B.P.E. held in Wyoming University (1959) summarised available knowledge of the condition. These results were itemised by Moulton et al (1961), who also discussed the clinical and pathological examinations of a herd affected by A.B.P.E. in California. In this outbreak, pulmonary disease appeared in October in cattle moved 10 days previously on to lush, fertilised, irrigated pasture they had grazed the previous spring. On one field, 25 of 250 animals were ill and 14 of these died after an illness of up to 5 days duration; on another pasture, 15 out of 300 were clinically ill and 6 died over 2 days. Adult animals 7-8 years old were usually

affected on this ranch and both sexes were believed to be involved, although few adult male animals were kept. Six animals were examined at postmortem, when alveolar epithelial hyperplasia, pulmonary oedema, interstitial emphysema and pulmonary eosinophilia were observed. In one cow there was alveolar interstitial fibrosis, but it was said that this cow had fewer clinical signs than most in the herd.

A further investigation of A.B.P.E. was made by Moulton et al (1963) and hyaline membranes were mentioned in the pulmonary pathology. Negative aetiological findings resulted from intradermal injection of plant allergens, virus isolation attempts, bacteriological examination and toxin studies (Moulton et al 1961), rumen gas analysis and indirect fluorescent antibody tests for antigen: antibody reactions in the lung (Moulton et al 1963).

Blake and Thomas (1971) provided a further account of A.B.P.E. in Utah and recorded cases in spring and autumn, when there was movement from poor to lush pastures on each occasion.

The most useful reports are those of Moulton et al (1961; 1963) and Blake and Thomas (1971).

Tucker and Maki and Maki and Tucker (1962) detailed attempts to provoke outbreaks of acute pulmonary emphysema under controlled conditions. Over 5 years, between 30 and 50 cows and calves were purchased each spring and moved to a summer pasture about the 1st June. The upland pasture they grazed was typical of that in the region. In late August or early September they were moved to a lush, irrigated, lowland pasture. Clinical disease developed in each year to varying degree. An attempt was made to protect animals by giving anti-toxin to C. welchii types A, B, C and D. Some protection was said to follow B, C and D in combination, but this was not significant at the 5% level.

These experiments confirmed the field observations that cattle became ill after a change of pasture, but did not provide any clue to the aetiology.

Respiratory disease and mouldy feeds

Gibbons (1962) reviewed the "new pneumonia complex" in cattle and quoted a classification of this complex into 4 entities made by van Kruiningen (table 2). He allowed that pulmonary emphysema and pulmonary adenomatosis might be a single disease or that these two diseases and 'bronchiolitis obliterans' were all three manifestations of the same condition. Gibbons compared the pulmonary lesions of "bronchiolitis obliterans" to silo-filler's disease of man. This is an often fatal condition caused by inhalation of oxides of nitrogen, coming off as fumes from grass or grain silos. The situations in which this type of disease occurs in man are largely accidental and it is unlikely that such events would commonly arise in housed or grazing cattle. Bronchiolitis obliterans is also a feature of farmer's lung in man and cattle and this disease has occurred under similar circumstances to van Kruiningen's 'bronchiolitis obliterans'. It would seem more logical that pulmonary disease in indoor cattle would develop from dust of mouldy food rather than toxic gases. One report of 'silo-filler's disease' in dairy cattle (Haynes 1963) must be considered with caution. In this outbreak there was no evidence that oxides of nitrogen were involved nor is there mention of mould. The link with silo-filler's disease of man was conjectural and ill-advised on the evidence presented.

Pulmonary adenomatosis is an acute, non-infectious respiratory disease, characterised clinically by sudden onset and short duration and pathologically by pulmonary emphysema, oedema and alveolar epithelial hyperplasia (Seaton 1957). The disease was reported in cattle feeding on mouldy foodstuffs (Monlux et al 1953) such as corn stalks and sweet potatoes; but Seaton (1957) claimed to see cases in pastured cattle not exposed to mouldy feed.

Seaton (1958) carried out an extensive investigation of pulmonary adenomatosis in Iowa; an earlier report of this condition in that state was given by Monlux et al (1955). Seaton (1958) examined animals from herds affected by pulmonary adenomatosis at postmortem and the pulmonary lesions were similar to those noted by Griner (1963) and Moulton et al (1961) in A.B.P.E. except

by H.J. Van Kruiningen, D.V.M.; N.Y. State Veterinary College

Etiology: Lush feeds, mold, silage, worms.

Common signs: Increased TPR, subcutaneous emphysema, anorexia.

Lung	Proliferative	Verminous	Bronchiolitis	Acute
Pathology	Pneumonia (Adenomatosis)	Proliferative Pneumonia	Obliterans	Pulmonary Emphysema
Feed	Aftermath Silage Moldy	Pasture	Silage Moldy hay	Aftermath Kale, rape Sweet potatoes
Onset	Acute	Acute	Chronic	Acute
Morbidity	Low	High	High	High or low
Signs	Dyspnea	Dyspnea	Dyspnea Cough	Dyspnea Expiratory grunt
Season	Later summer Early fall	Late summer Early fall	January through April	Late summer Early fall
Age	All (older)	All	Older	Older
Housing	Barn Pasture	Pasture	Barn	Pasture
Duration	1-2 days	1-2 days	1 week	2-10 days
Mortality	High	High	Low	Low
Gross P.M.	Big, heavy wet lungs	Big, heavy wet lungs	Big, spongy, dry lungs with diffuse nodules	Emphysematous lungs
Therapy	Atropine 1-2 G. Change feed	Atropine 1-2 G. Parasite control	Corticoids in large doses; change feed ventilate silage	Atropine Adrenalin Antihistamines Change feed

Table (2) The New Pneumonia Complex (from Gibbons W.
Mod. Vet. Pract. (1962) 43, 34.)

that alveolar epithelial hyperplasia was more extensive and dramatic in 53
Seaton's cases. Seaton considered A.B.P.E. and pulmonary adenomatosis were
identical and claimed that histological sections of A.B.P.E., examined by
him, had alveolar epithelial hyperplasia similar to pulmonary adenomatosis.

Seaton (1958) investigated his cases by questionnaire survey (to
ascertain epidemiology and herd history), clinical examination of an
unspecified number of field cases and postmortem inspection of one animal
from each of 10 herds, with other histological specimens submitted from time
to time. The only aspect of this report which may be reliable would seem to
be the pathology, since it is not clear whether the epidemiology, history
and clinical signs were the result of personal observation or were the views
of others. Despite the detailed information available in this paper, there is
no definite example in which an adequate clinical history, epidemiological
background, diet, and pulmonary lesions were specified for any group of
animals. Seaton stated that the disease was seen in animals ranging from a
calf of 2 months old to a cow 13 years old, including beef and dairy breeds,
males and females. The disease occurred at all seasons, especially late
summer and autumn. Rations were only briefly detailed. There was a common
pulmonary pathology to these respiratory syndromes arising in very different
epidemiological circumstances, but there was no proof that this was one
syndrome and subsequent evidence would support the view that several syndromes
were involved in pulmonary adenomatosis (c.v.).

Vickers et al (1960) also reported pulmonary adenomatosis in cattle
which were fed on mouldy sweet potatoes, mouldy hay, or lush pasture. The
pulmonary lesions included alveolar epithelial proliferation and interstitial
emphysema. Only 4 animals (of nine recorded) were examined at postmortem by
"laboratory personnel", the others were inspected by practitioners. There
was no full statement of the history of each herd, the history and signs of
animals examined from such herds, the pulmonary lesions in each animal, nor
the amount of material examined and the extent of the lesions. This report
indicates that respiratory disease may be found in animals under various

systems of management; these sometimes present as acute respiratory distress, which may be associated with interstitial emphysema.

The original description of pulmonary adenomatosis made note of the fact that the animals were feeding on mouldy sweet potato (Monlux et al 1953). It has recently been found that a lung oedema factor, capable of producing death acutely in mice and laboratory animals, can be isolated from mouldy sweet potato infected with Fusarium javanicum (Wilson et al 1970). Mouldy sweet potato (Ipomoea batatas) was known to be poisonous to cattle and animals died of respiratory disease 2-5 days after ingestion (Hansen 1928). The condition has also been a problem in Japan (Hiura 1943; Kubota et al 1952). An extensive outbreak in America was detailed by Peckham et al (1972), when the condition was reproduced by feeding homogenised sweet potato cultures infested with F. javanicum. The sweet potato itself produces the toxins ipomeamarone, ipomeamaranol and a lung oedema factor in response to the fungal infection, so the condition is not a hypersensitivity to moulds of the farmer's lung type (Wilson et al 1970; 1971).

The aetiology of pulmonary adenomatosis due to mouldy sweet potato is now known and the condition must be distinguished from pulmonary adenomatosis in cattle after pasture change and the condition in housed beef cattle or animals exposed to mouldy hay. It is possible that the group of cases considered as pulmonary adenomatosis by Seaton (1958) and Vickers et al (1960) might comprise several distinct syndromes, including sweet potato poisoning; farmer's lung; A.B.P.E.; A.I.P. in barley-beef-type feedlot calves and even parasitic bronchitis.

Nitrogen peroxide and pulmonary disease.

Seaton (1957) was struck by the similarity between silo-filler's disease and pulmonary adenomatosis in cattle. He exposed two cows to 'nitrogen dioxide and associated oxides' and recorded the pulmonary lesions, which were so similar to those of silo-filler's disease and pulmonary adenomatosis that "it leads one to believe that the aetiology of these

diseases is similar if not identical". He went on to suggest that
55
fermentation in the rumen might produce NO₂, like fermentation in the silo,
and that gas might be absorbed through the rumen or during eructation.

Seaton (1958) exposed a steer to nitrogen dioxide by stomach tube
for some 32 days without satisfactory result. Cutlip (1967) introduced
NO₂ by intra-rumen cannula into several heifers for various periods of
time, but did not produce lesions of A.B.P.E. - rather fatalities from
methaemoglobinaemia. Cutlip (1966) gave NO₂ by tracheotomy tube or direct
inhalation to heifers and concluded that NO₂ was probably not involved in
the pathogenesis of A.B.P.E.. NO₂ gas was not found in the rumen of cases
of A.B.P.E. (Moulton et al 1963).

Silo filler's disease of man is an accidental intoxication by NO₂
gas. The disease does not appear to have been clearly demonstrated in cattle.

Incidents recorded as NO₂ poisoning could also be farmer's lung or
another pulmonary disease (Haynes 1963; Blood 1962). The association
between NO₂ and A.B.P.E. has been shown to be speculative.

Pulmonary disease and tryptophan administration

Administration of L, or DL-tryptophan or 3 methyl-indole and
indoleacetic acid to cattle has been demonstrated to produce a pulmonary
condition with many points in common with A.B.P.E. (Dickinson, Spencer and
Gorham 1967; Monlux, Cutlip and Estes 1970; Dickinson 1970; Dickinson and
Piper 1971; Carlson, Dyer and Johnson 1968; Carlson, Yokoyama and Dickinson
1972). This syndrome is reviewed below and further experimental work
provided. There has been no conclusive demonstration of the application of
these results to A.B.P.E. or fog fever in animals at grass, although there
are strong hypothetical connections.

It may be that this experimental syndrome has no relevance to the
pasture disease. Similar lesions to A.B.P.E. and fog fever may be produced

by Bordetella pertussis administration and sweet potato poisoning. Final proof of the implication of tryptophan and related compounds in fog fever must include demonstration of such compounds in grass at significant levels, followed by their ingestion and release.

Summary

No one has yet attempted to distinguish and define the respiratory syndromes in cattle which present with acute signs and sudden onset dyspnoea in the U.S.A.. It appears likely that a detailed investigation might break down the heterogeneous group loosely known as A.B.P.E. into:-

- 1) A.B.P.E. in cattle at pasture
- 2) Farmer's lung
- 3) Diffuse fibrosing alveolitis
- 4) Sweet potato poisoning
- 5) 'A.I.P.' in housed calves
- 6) Parasitic bronchitis
- 7) NO₂ gas poisoning
- 8) Tryptophan and other chemical induced disease
- 9) 'Milk allergy' (v.inf.).

It is unlikely that any efforts to determine the aetiologies of these conditions will be successful if the diseases are continually confused with each other and other forms of pneumonia.

THE ACUTE RESPIRATORY DISTRESS SYNDROME IN EUROPE:

A REVIEW OF THE LITERATURE

THE ACUTE RESPIRATORY DISTRESS SYNDROMEIN EUROPE

Acute respiratory distress in adult cattle associated with emphysema and pulmonary oedema has been reported on many occasions in several European countries over many years. In France, Delalande et al (1830), Schijns and Belleflamme (1936), Perrier (1950), Bouard (1953), and Foucher (1960) were among those who recorded such diseases associated with aftermath-type pastures. In Holland, van Gils (1951a; 1951b; 1956) and Weisman (1970) investigated pulmonary emphysema or "fog fever". The syndrome has also been frequently observed in Belgium, Germany and Italy.

Reviews of the literature were given by Perrier (1950), Maki (1963) and Geisel (1969).

Comparisons between fog fever in Britain, A.B.P.E. in the U.S.A. and an assortment of respiratory diseases in Europe form a customary introduction to reviews of the literature pertaining to these diseases. The impression has arisen that these various diseases are all very similar; this opinion does not appear to be supported by any detailed clinical, epidemiological and pathological comparison.

In Europe, there seems to be a syndrome involving cattle recently moved to fresh, improved pasture (see Perrier 1950; Foucher 1960), but it is not possible to assess the role of simple parasitic bronchitis in these incidents. Just as fog fever became confused by the addition of epidemiologically and pathologically distinct conditions, so the pasture disease in Europe has been complicated by additions to the original descriptions.

Respiratory disease in cattle exposed to mouldy hay was reported by Bruins (1953) and was considered by Maki (1963) to be part of 'bovine pulmonary emphysema'. Another record of a respiratory disorder in housed cattle in Switzerland (Pankhauser and Luginbuhl 1960) was later considered to be 'chronic fog fever' (Mackenzie 1966) despite many differences in

Major contributions to the literature are those of Fankhauser and Luginbuhl (1960); Luginbuhl (1960a & b); Geisel (1969); and Weisman (1970), although there are many other chronicles of the clinical syndromes (reviewed by Maki 1963).

Fankhauser and Luginbuhl (1960) and Luginbuhl (1960 a & b) gave detailed descriptions of 'Urner pneumonia', a respiratory disease of cattle housed indoors in Switzerland. 'Urner pneumonia' was a sudden onset respiratory disorder which affected cattle feeding on hay indoors during late autumn through to May. Cases were seen most frequently when bad hay was being fed and animals with relapsing pneumonia occasionally remained ill into the summer. Most animals were eventually sold for economic reasons during the long illness, although some were slaughtered in the acute stages. The clinical signs were severe coughing, dyspnoea, increased respiratory rate, variable pyrexia, fall in milk yield and loss of weight.

At postmortem, three phases of disease were recognised:-

1) Alveolar and interstitial emphysema

Hyaline membranes and focal alveolar epithelial hyperplasia

Interstitial cellular infiltration by plasma cells and lymphocytes

2) Alveolar epithelial hyperplasia and alveolar septal fibrosis

Plasma cell and lymphocyte infiltration of alveolar septa

Few hyaline membranes

3) Squamous metaplasia of bronchi

Severe interstitial fibrosis and alveolar epithelialisation

Marked cellular invasion of alveolar septa.

Urner pneumonia was also detailed by Herzog (1970) and Nicolet et al (1969).

The clinical features and postmortem lesions of Urner Pneumonia have many differences from those of classical fog fever; the most

significant being marked cough, the indoor exposure to bad hay, the cellular infiltration of the alveolar septa and the severe fibrosis. Although epithelioid granulomata were not demonstrated, Urner pneumonia resembles farmer's lung and some aspects of diffuse fibrosing alveolitis in man (Crofton and Douglas 1969); the disease is strikingly similar to bovine extrinsic allergic alveolitis and diffuse fibrosing alveolitis (Pirie et al 1971a, Pirie and Selman 1972). The Swiss workers now attribute Urner pneumonia to an extrinsic allergic alveolitis of farmer's lung type (Luginbuhl 1971; Nicolet et al 1972). It is interesting to note that Nicolet et al (1972) found precipitating antibodies to M. faeni in only 49% of clinical cases of Urner pneumonia (the typical clinical symptoms were not specified). The reasons for this were discussed. However, it was admitted that the diagnosis may have been incorrect, since only 4 of 39 cases were examined histologically. Not all cases of bovine fibrosing alveolitis have detectable precipitins to M. faeni in their sera and, in man, not all cases of fibrosing alveolitis are the result of chronic farmer's lung. There is a strong possibility that the Swiss reports may include two syndromes - farmer's lung and diffuse fibrosing alveolitis (D.F.A.).

The concept of chronic fog fever with fibrosis is first mentioned in Britain by Mackenzie (1965). It is not clear whether he is discussing possible lesions in fog fever or describing cases encountered personally. There do not appear to be other published descriptions of this chronic syndrome in Britain.

Geisel (1969) investigated acute pulmonary oedema and emphysema (APE) in cattle presented routinely at slaughter houses or for postmortem in Germany. Fifteen cases of APE were diagnosed in 140 lungs examined and the disease was divided into acute, subacute and chronic stages histopathologically. The pulmonary lesions were interstitial oedema, hyaline membranes, proliferation of alveolar epithelium and histiocytic infiltration of alveolar septa; these lesions were considered to be evidence of

hypersensitivity. The clinical aspects and differentiation from parasitic bronchitis were not summarised. Geisel found these lung lesions to be similar to those of the Hamman-Rich syndrome and farmer's lung. The Hamman-Rich syndrome in man is a somewhat diverse disease entity now more commonly known as diffuse fibrosing alveolitis. "It is characterised pathologically by a diffuse inflammatory process in the lung beyond the terminal bronchiole having as its essential features:-

- 1) Cellular thickening of the alveolar walls showing a tendency to fibrosis

- 2) The presence of large mononuclear cells, presumably of alveolar origin, within the alveolar spaces", (Scadding and Hinson 1967).

Liebow et al (1965) differentiated "desquamative interstitial pneumonia", in which marked desquamation of cells into the alveolar spaces was a feature, from D.F.A., but Scadding and Hinson (1967) considered these to be parts of a continuous pathological spectrum. In the form of disease originally described by Hamman and Rich (1944) fatal outcome occurred within six months after onset of signs, but in the chronic form of the disease the course might be several years (Crofton and Douglas 1969). Geisel did not describe this typical fibrosis and desquamation in his cases.

There are clinical and pathological differences between D.F.A. and farmer's lung of man and animals and fog fever as seen in Britain. Geisel worked with autopsy specimens and in the absence of clinical history might well have been describing several syndromes of cattle. Geisel also compared his cases to farmer's lung and, although there were similarities, did not mention infiltration of alveolar walls by polymorphs, lymphocytes and plasma cells; epithelioid granulomata; interstitial fibrosis or bronchiolitis obliterans; lesions regarded as typical of farmer's lung in man (Crofton and Douglas 1969). These animals had pulmonary lesions similar to some aspects of fog fever, D.F.A., farmer's lung or post-patent husk, but there was insufficient information to take the differential diagnosis any further.

Weisman (1970) investigated fog fever in the Netherlands and 62
expanded the work of Michel (1954). Weisman defined "fog fever" as
"dyspnoea and an acute and fairly long lasting emphysema". He infected
33 parasite free cattle, aged from 2 to 204 months, with doses ranging from
3200 to 92,000 larvae of D. viviparus. Twenty of these 33 were again orally
infected, after an interval of 4-24 months, with 34,200 - 121,000 larvae.
Nine of these twenty were further infected, after another 5-10 months, with
35,000 - 114,000 larvae. A single animal was infected yet again, after
another 12 months, with 96,000 larvae. One recovered animal died in a few
minutes after intravenous challenge with lungworm antigen. Fourteen of the
twenty animals orally reinfected developed 'fog fever' after at least one
challenge; two out of 20 developed 'fog fever' during the first infection.

Postmortems were performed on the 14 cattle, of which 3 were
infected once, 5 twice, 5 three times and 1 animal four times. Animals
were killed several months after infection or reinfection. One cow killed
after the 3rd infection had pulmonary emphysema and oedema, and these
lesions were also found in a calf which died 4½ months after the 1st
infection. Ten of the remaining twelve animals were found to have diffuse
alveolar emphysema, which was of severe degree in one and only slight in
the other nine. All 14 animals exhibited 'chronic bronchitis' and
bronchiolitis, peribronchitis and interstitial pneumonia.

It is clear that an acute pulmonary disorder did arise in these
cattle. The relationship between this and fog fever in Britain as described
by Barker (1948), Begg and Whiteford (1948) and Leslie (1949) is not
apparent. Any differences between this syndrome in the Netherlands and the
reinfection phenomenon (Jarrett et al 1960, Pirie et al 1971c) are not
obvious. The animals which were postmortemed were examined when the
pulmonary condition had subsided, often several months later. The lesions
of emphysema and oedema appear to have been slight, possibly agonal, and
not as dramatic as those associated with fog fever in Britain. The
characteristic nodules of reinfection were not mentioned, either because

they were unappreciated or had disappeared at the time of postmortem. Hyaline membranes and alveolar epithelialisation were not described. The initial doses of larvae which were used to infect animals were greater, in many cases very much greater, than those needed by Jarrett, McIntyre and Urquhart (1957) to produce disease. Two animals, aged 14 and 18 months, given approximately 49,000 larvae were subsequently reinfected many months later. Jarrett, McIntyre and Urquhart (1957) found that calves given 50,000 larvae did not survive more than 18 days post infection. This suggests that the cattle previously mentioned resisted the infection or that the larvae had low viability. Larval infectivity was not adequately controlled.

Five field cases, which had been diagnosed as clinical fog fever cases, were subsequently infected with lungworms on 3 or 4 occasions at intervals of 2-10 months using 82,000-127,000 larvae as a challenge dose. One particular cow was infected with 96,000, 110,000, 202,000 and 320,000 larvae in this experiment. Slight alveolar emphysema and oedema were found at postmortem several months later. Reinfection nodules were not described.

Fifty field cases suffering from clinical fog fever were investigated. These animals originated from 23 farms and 84% of cases occurred in summer and autumn, only 16% in the spring. Four animals died and were postmortened; acute emphysema and oedema were revealed in the lungs. One animal killed after clinical signs disappeared had slight pulmonary oedema.

The diagnosis of fog fever was made when certain arbitrary clinical conditions were fulfilled and confirmed by the presence of emphysema and oedema in the lungs. Weisman's clinical definition only fulfils part of the description of the disease in Britain and the two lung lesions alone cannot be described as "characteristic". The lung pathology of the acute syndrome he induced would have been of the utmost importance. Since this is not available, these animals can only be regarded as exhibiting various manifestations of the reinfection phenomenon with D. viviparus, the pathology of which is different from that of fog fever (Jarrett et al 1960; Michel and Mackenzie 1965, Pirie et al 1971c).

There is no evidence that all the fog fever-like conditions described in European cattle have the same aetiology or are part of the same syndrome. Certain common features are the presenting clinical sign of acute dyspnoea and some aspects of the pathology. These conditions have not yet been accurately defined.

A FIELD STUDY OF FOG FEVER AND ACUTE RESPIRATORY
DISTRESS SYNDROMES IN CATTLE

INTRODUCTION

FOG FEVER AND ACUTE RESPIRATORY DISTRESS SYNDROMES IN ADULT CATTLE

RESPIRATORY DISEASE IN ANIMALS IN THEIR FIRST GRAZING SEASON

RESPIRATORY DISEASE IN ANIMALS IN THEIR SECOND GRAZING SEASON

RESPIRATORY DISEASE IN ANIMALS HOUSED INDOORS

INTRODUCTION TO FIELD STUDY

Letters were sent to all veterinary practices in Scotland and selected ones in northern England in June 1969-72. The letter invited practitioners to submit cases they had diagnosed as fog fever to us for further examination. In the event, only a small number of practitioners consistently supplied animals.

Once the diagnosis of fog fever had been made, the veterinary surgeon arranged for the affected animal to be admitted to the Veterinary School. In many instances a dead animal was sent initially; then a farm visit and clinical examination of the herd was made as soon as practicable, when every effort was made to purchase at least one other animal affected by the respiratory disease. All animals admitted to the Veterinary School were clinically examined, subsequently slaughtered and examined at postmortem.

At the end of 1969, it was obvious to us that different veterinary surgeons applied different criteria for the diagnosis of fog fever and that the animals referred had varied pulmonary pathology, which had often presented with similar clinical signs.

No age restriction was mentioned in our letters and all ages of animal from young calves to aged cows were admitted. After clinical examination, it was often apparent that another diagnosis than fog fever was immediately obvious.

The animals examined were initially divided into 4 groups on the basis of their age and management:-

Group 1 Adult cattle

Group 2 Animals under one year old or at grass for the first time

Group 3 Animals in their second grazing season

(usually 12-24 months of age)

Group 4 Animals under one year of age housed indoors

The numbers of animals in each group and the diagnosis in each case are given in the following pages. Details of individual cases are set out in appendices 1-5.

A summary of the main clinical and epidemiological findings precedes the report of the pulmonary lesions of each group; the full clinical and epidemiological data will be the subject of further papers (Selman et al - to be published).

All the animals numbered below were submitted to us as examples of 'fog fever'. The respiratory conditions diagnosed at postmortem and the numbers of animals affected in each group are indicated.

Group 1: adult cattle

	<u>Number of cattle examined</u>
Fog fever	43
Acute pulmonary oedema and interstitial emphysema	2
Reinfection husk	6
Diffuse fibrosing alveolitis	10
Bovine extrinsic allergic alveolitis	2
Thrombosis of the posterior vena cava with pulmonary thrombo-embolism	3
Chronic suppurative pneumonia	6
Miscellaneous	5
	<u>Total 77 animals</u>

In addition, 7 animals affected by fog fever were not immediately examined at the time of illness; they were retained alive for experimental purposes.

Fog fever was diagnosed in 43 of the 77 animals postmortemed
and in 50 of the 84 cases admitted.

Group 2 : animals under one year old or in their first grazing season.

Pre-patent parasitic bronchitis	4
Patent parasitic bronchitis	18
Post-patent parasitic bronchitis	22
<u>Total 44 animals</u>	

Group 3: animals in their second grazing season.

Post-patent parasitic bronchitis	6
<u>Total 6 animals</u>	

Parasitic bronchitis was the only respiratory disease in 50 animals under 2 years of age at grass for the first or second time.

Group 4: animals housed indoors.

Atypical interstitial pneumonia	6
Acute bronchopneumonia and chronic suppurative pneumonia	6
Post-patent parasitic bronchitis	1
<u>Total 13 animals</u>	

The different pulmonary lesions were graded after histological or gross examination in order to quantitate their degree and extent. For microscopical examination, tissues from the apical lobes were identified separately and samples were regularly taken from specified sites in the bronchial tree and from adjacent pulmonary tissue. These representative samples, together with additional material wherever it was necessary, enabled the histological changes to be evaluated in the different lobes of the lung. In practice, about 60 blocks of tissue were examined in each case. The lesions apparent on gross inspection were classified according to their severity in each lobe and the number of lobes affected.

Interstitial emphysema An estimate was made on gross inspection of the lungs and the categories were:-

- 1+ :- diffuse overinflation of alveoli with local, segmental, interstitial emphysema in one lobe of each lung.
- 2+ :- as in 1+ but affecting more than one lobe of each lung.
- 3+ :- as in 2+ but with large bullae present also.

Pulmonary oedema After a gross examination this was categorised:-

- 1+ - mild - oedema fluid expressed from lung
- 2+ - moderate
- 3+ - severe - oedema fluid running freely from lung

Hyaline membranes Microscopical examination enabled this lesion to be graded:-

- 1+ :- present in some acini in some lung lobes.
- 2+ :- present in the majority of acini in all lobes.

Alveolar epithelial hyperplasia Histological examination was used to categorise this lesion:-

- 1+ :- short rows of 2-5 cuboidal cells on the alveolar septa of a minority of alveoli in some lung lobes.
- 2+ :- short rows or ribbons of cuboidal cells in the majority of alveoli in some lung lobes.
- 3+ :- a complete cuboidal cell lining of the majority of alveoli in all lung lobes.

Eosinophil infiltration of the lungs

This was graded mild, moderate or marked, when present, after histological examination of carbol chromotrope stained sections from the specified levels in the bronchial tree and lung.

Globule leucocytes

Globule leucocyte occurrence in the bronchial tree was graded occasional, frequent or very frequent, when present, after histological examination of corrosive formol fixed, H & E or Mallory stained sections from the specified levels in the bronchi.

FOG FEVER AND ACUTE RESPIRATORY DISTRESS SYNDROMES IN ADULT CATTLE

FOG FEVER

DIFFUSE FIBROSING ALVEOLITIS AND EXTRINSIC ALLERGIC ALVEOLITIS

THROMBOSIS OF THE POSTERIOR VENA CAVA WITH PULMONARY THROMBO-EMBOLISM
AND HAEMOPTYSIS

PULMONARY DISEASE DUE TO REINFECTION WITH DICTYOCAULUS VIVIPARUS

ACUTE PULMONARY OEDEMA AND INTERSTITIAL EMPHYSEMA

OTHER RESPIRATORY DISORDERS

DISCUSSION: RESPIRATORY DISEASE IN ADULT CATTLE

FOG FEVER

RESULTS OF THE FIELD STUDY

CLINICAL SIGNS, HISTORY AND EPIDEMIOLOGY

PATHOLOGY

BACTERIOLOGY

PARASITOLOGY

DOUBLE DIFFUSION TESTS FOR PRECIPITATING ANTIBODIES TO M. FAENI

DISCUSSION - clinical signs, history and epidemiology
 pathology
 parasitology
 fog fever and other pulmonary diseases
 fog fever and parasitic bronchitis
 aetiology

RESULTS OF THE FIELD STUDY

Fifty animals were believed to be affected by fog fever after our clinical examination and consideration of the herd history. Forty three of these animals were examined at postmortem immediately, the other seven were maintained indoors for experimental purposes. Nineteen of the 43 animals were admitted to the hospital alive, the other 24 died on the farm or in transit.

Fixed portions of lung were submitted as postal specimens in 2 of the 24 cases and in a further 4 instances the lungs, heart, liver and kidneys only were received; the rest of the animal was taken to a knackery. In all 24 cases the animal had died very quickly, usually before it could be examined alive by us. There were obvious differences in the pathology of the animals admitted dead and those slaughtered; the animals were therefore classified into 24 fatal cases and 19 non-fatal cases.

CLINICAL SIGNS, HISTORY AND EPIDEMIOLOGY

All 50 cattle affected by fog fever were adult, beef-type females and all developed a sudden onset, respiratory distress condition soon after a move from a poorer pasture to improved grazing in the autumn.

The full clinical and epidemiological findings in these cases will be given later (Selman et al 1974 - to be published), but the main features have been briefly considered below.

Age

All the cattle were adults, that is older than 2 years. The actual age has been given when possible (Tables 3, 4), but in many instances this was unknown.

Sex

There were no male animals (Tables 3, 4).

Breed

The number of each breed encountered is given in tables (5, 6). In all cases, including the Friesians, the animals were being managed as beef cattle in suckler herds and were not producing milk for dairy purposes. All the common beef breeds and their crosses are represented in these lists.

Season

All cases were seen in the period from the last week of August to the end of November; the majority were examined in September, October and November (Tables 3, 4 and Figs. 2, 3).

Time of onset

The disease always developed after movement to fresh pasture and the period between this change and first clinical signs varied from 1 to 21 days, but was mostly between 1 and 14 days (Fig. 4 and tables 3, 4).

Duration of illness

This ranged from less than one day to 17 days between first observation of signs and death (Fig. 5). The majority of non-fatal cases were apparently recovering clinically at the time of slaughter. Individual cases are detailed in tables(3,4). Fatal cases succumbed within 4 days (Fig. 6).

Pasture

Not all the animals developed clinical disease on aftermath but in all cases the cattle moved from a relatively bare pasture to an improved, well grown, richer grazing on which the grass was more abundant. In most instances this new grazing had been fertilised at least once earlier in the season. Two incidents occurred when the cows were eating Brassicacae - in one case, turnip tops and the other, rape.

Calves

Many animals had calves at foot, but these calves never developed acute respiratory signs. In some cases, coughing in these younger animals indicated parasitic bronchitis of mild degree and treatment had occasionally been given for this disease. Faecal samples contained small numbers (less than 100) of lungworm larvae in some cases.

Morbidity and mortality

Although there were 24 fatal cases, the proportion of these may have been exaggerated by transport to us, since several cows died in transit. It was noticed that some cattle died whilst walking from the field to the farm buildings for treatment or when they became excited after their calves

had been taken away. It is possible that if these cases had remained quietly in the field some may not have succumbed.

Most outbreaks were reported when one or more animals died after a short illness. Our examination, at this time, usually revealed other animals with a lesser degree of clinical signs; these animals were often not noticed by the farmer and he was reluctant to sell them in many cases.

Previous history

Only two cows had been affected by fog fever previously, in the opinions of their owners; more often, it was claimed that incidents of fog fever had occurred on the farm in previous years, before our survey. The 43 cattle examined at postmortem (and the other 7 cases) were derived from 30 outbreaks or incidents of fog fever. The years in which these outbreaks were investigated are indicated in Fig. (2).

Pasture change

All the cattle became ill soon after a change of pasture. The interval between the last pasture change and death or slaughter is given in each case in Fig.(7).

ANIMAL	AGE	SEX	BREED	MONTH OF DEATH	TIME OF ONSET AFTER MOVEMENT (DAYS)	DURATION OF ILLNESS (DAYS)	TIME BETWEEN MOVEMENT AND DEATH (DAYS)
1	Adult	F	Angus	October	1	1	2
2	Adult	F	Hereford	September	2	1	3
3	Adult	F	Hereford	September	3	1	4
4	Adult	F	Hereford	October	1	3	4
5	Adult	F	Hereford	September	2	3	5
6	3y	F	Galloway	September	4	2	6
7	6y	F	Hereford	September	3	3	6
8	Adult	F	Hereford	November	6	1	7
9	Adult	F	Blue/grey	October	6	1	7
10	8y	F	Galloway	October	6	2	8
11	5y	F	Hereford	October	5	3	8
12	Adult	F	Hereford	October	6	2	8
13	Adult	F	Hereford	September	6	2	8
14	4y	F	Hereford	October	7	2	9
15	5y	F	Hereford	October	8	Found dead	9
16	8y	F	Shorthorn	October	7	2	9
17	Adult	F	Hereford	November	6	3	9
18	Adult	F	Hereford	October	6	4	10
19	3y	F	Hereford	November	10	1	11
20	3y	F	Hereford	November	10	1	11
21	7y	F	Blue/grey	November	8	4	12
22	Adult	F	Galloway	November	15	1	16
23	3y	F	Hereford	October	14	3	17
24	5y	F	Galloway	October	21	1	22

Table (3) Fog fever : significant clinical and epidemiological details of 24 fatal cases.

ANIMAL	AGE	SEX	BREED	MONTH OF DEATH	TIME OF ONSET AFTER MOVEMENT (DAYS)	DURATION OF ILLNESS (DAYS)	TIME BETWEEN MOVEMENT AND DEATH (DAYS)
25	5y	F	Hereford	September	2	1	3
26	5y	F	Galloway	October	3	2	5
27	2y-3y	F	Hereford	September	3	2	5
28	6y	F	Hereford	September	3	3	6
29	Adult	F	Hereford	October	2	5	7
30	Adult	F	Hereford	September	3	5	8
31	8y	F	Blue/grey	August	2	6	8
32	Adult	F	Hereford	October	7	2	9
33	7y	F	AAx	October	4	6	10
34	5y	F	Hereford	October	8	3	11
35	5y	F	Hereford	September	10	2	12
36	Adult	F	Shorthorn	September	6	7	13
37	Adult	F	Blue/grey	October	11	6	17
38	5y	F	Hereford	September	10	7	17
39	Adult	F	Galloway	October	14	4	18
40	Adult	F	Blue/grey	October	14	4	18
41	Adult	F	Hereford	October	2	17	19
42	Adult	F	Shorthorn	November	12	8	20
43	Adult	F	Shorthorn	November	13	9	22

Table (4) Fog fever: significant clinical and epidemiological details of 19 non-fatal cases

BREED	No. of CASES
Hereford-type	26
Angus/Galloway	8
Shorthorn	4
Blue-grey	5

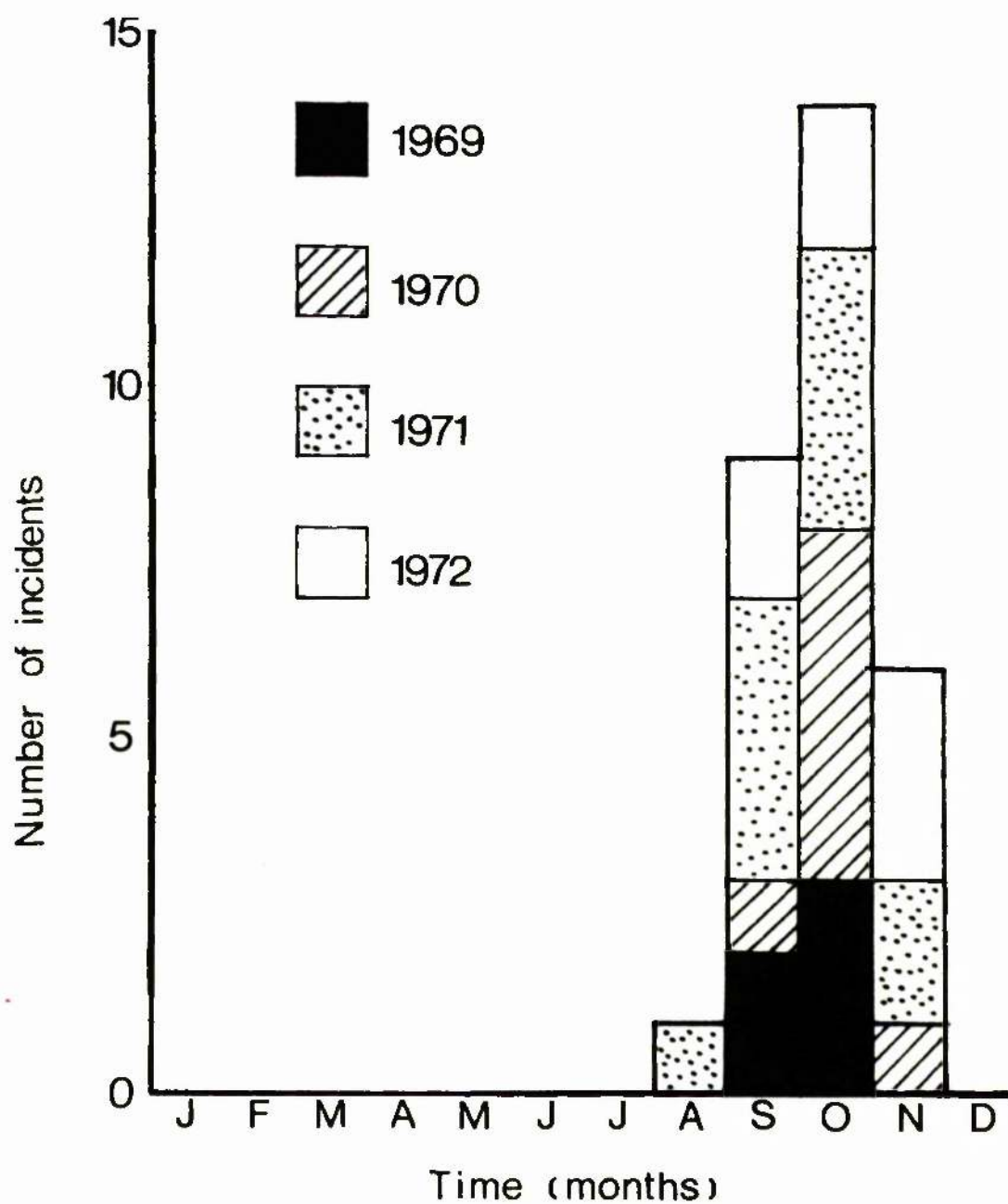
(Table 5)

Fog fever: breed incidences in 43 clinical cases of the disease examined at postmortem.

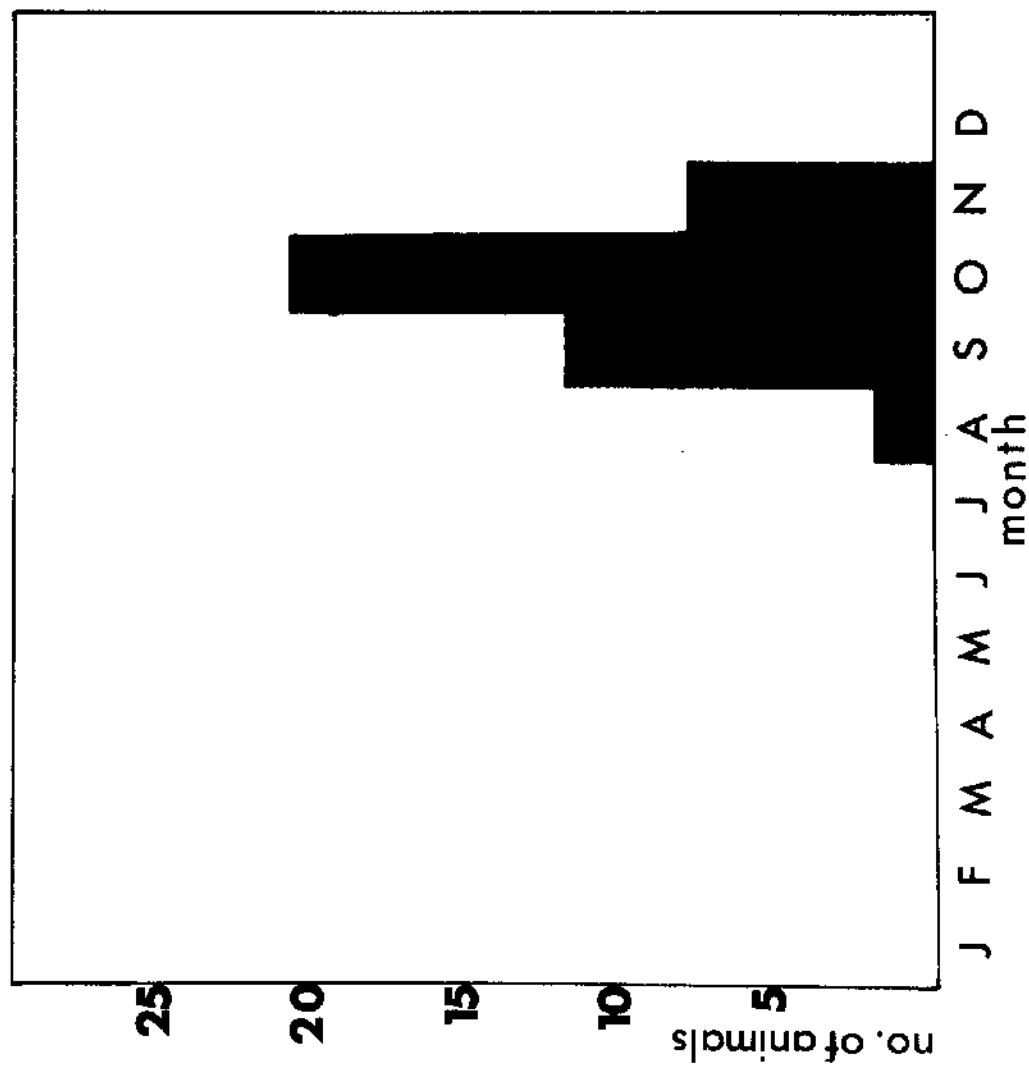
BREED	No. of CASES
Hereford-type	30
Angus/Galloway	8
Shorthorn	4
Blue-grey	6
Friesian	2

(Table 6)

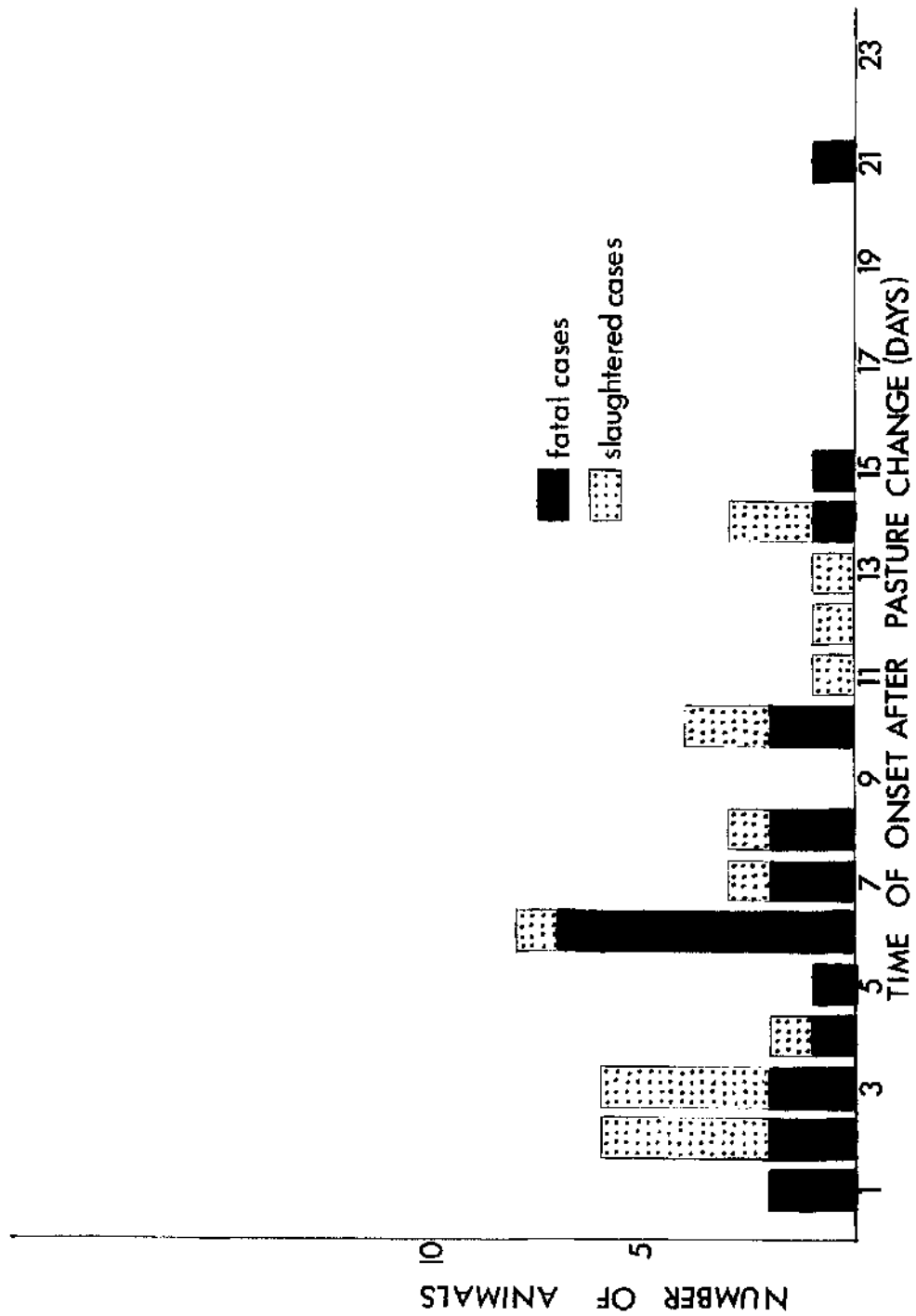
Fog fever: breed incidences in 50 clinical cases examined.



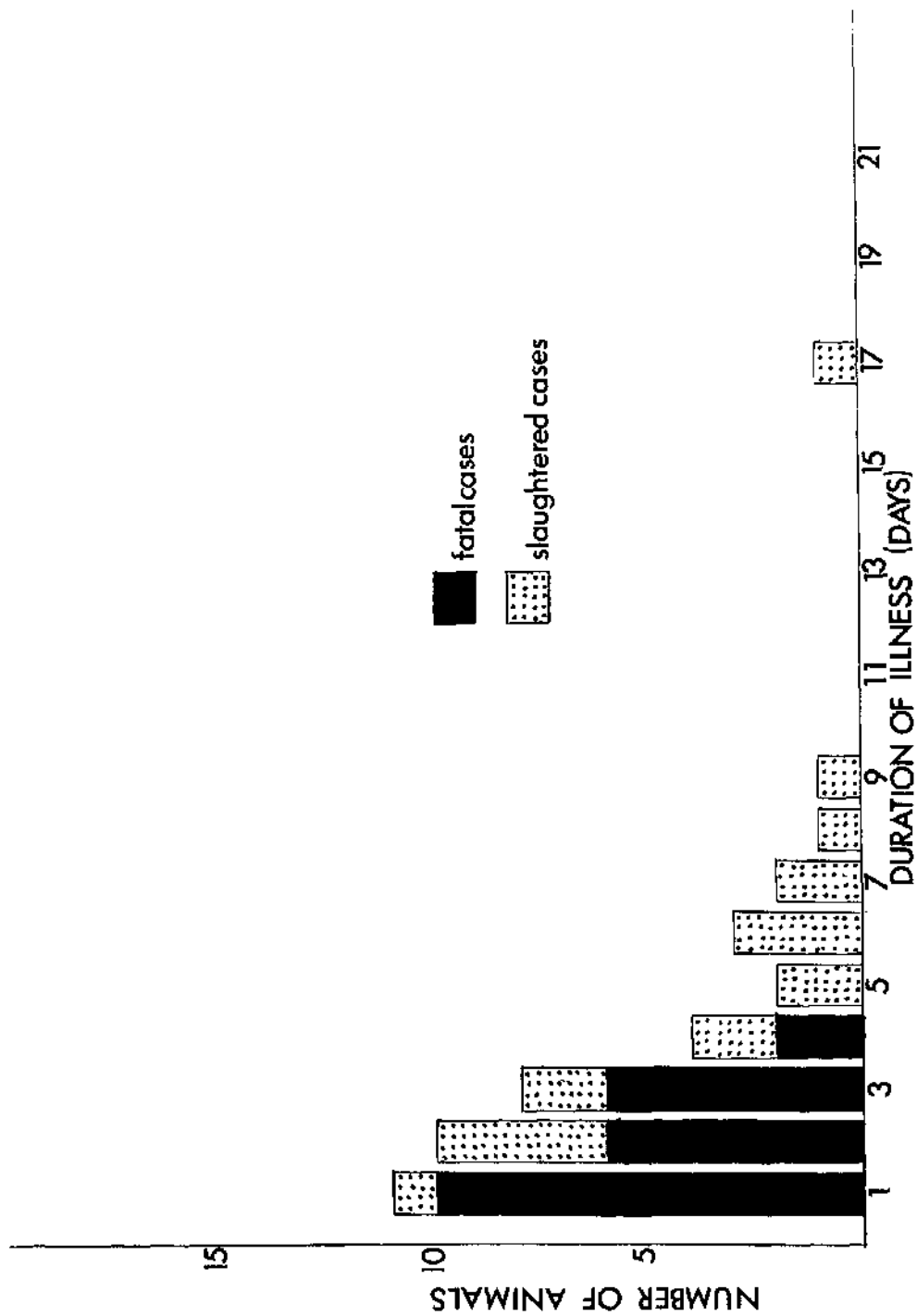
(Fig. 2) Fog fever: the month of the year in which 30 incidents of fog fever were investigated during 1969-1972.



(Fig. 3) Fog fever: month of year in which clinical cases were encountered.



(Fig. 4) Fog fever: the time of onset of clinical signs after last pasture change in 43 cases.



(Fig. 5). Fcg fever: Duration of illness (from first signs to death or slaughter) in 43 cases.

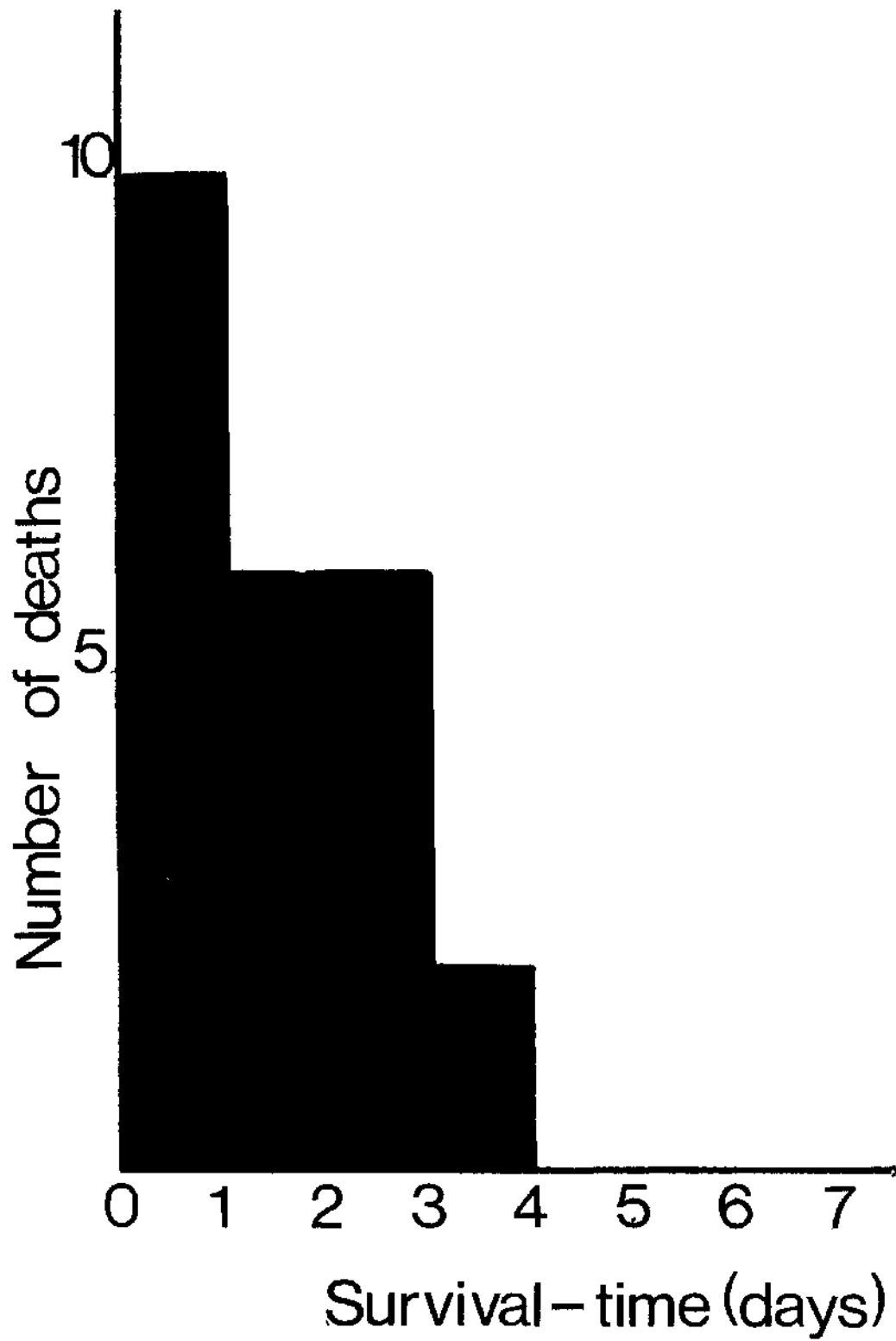
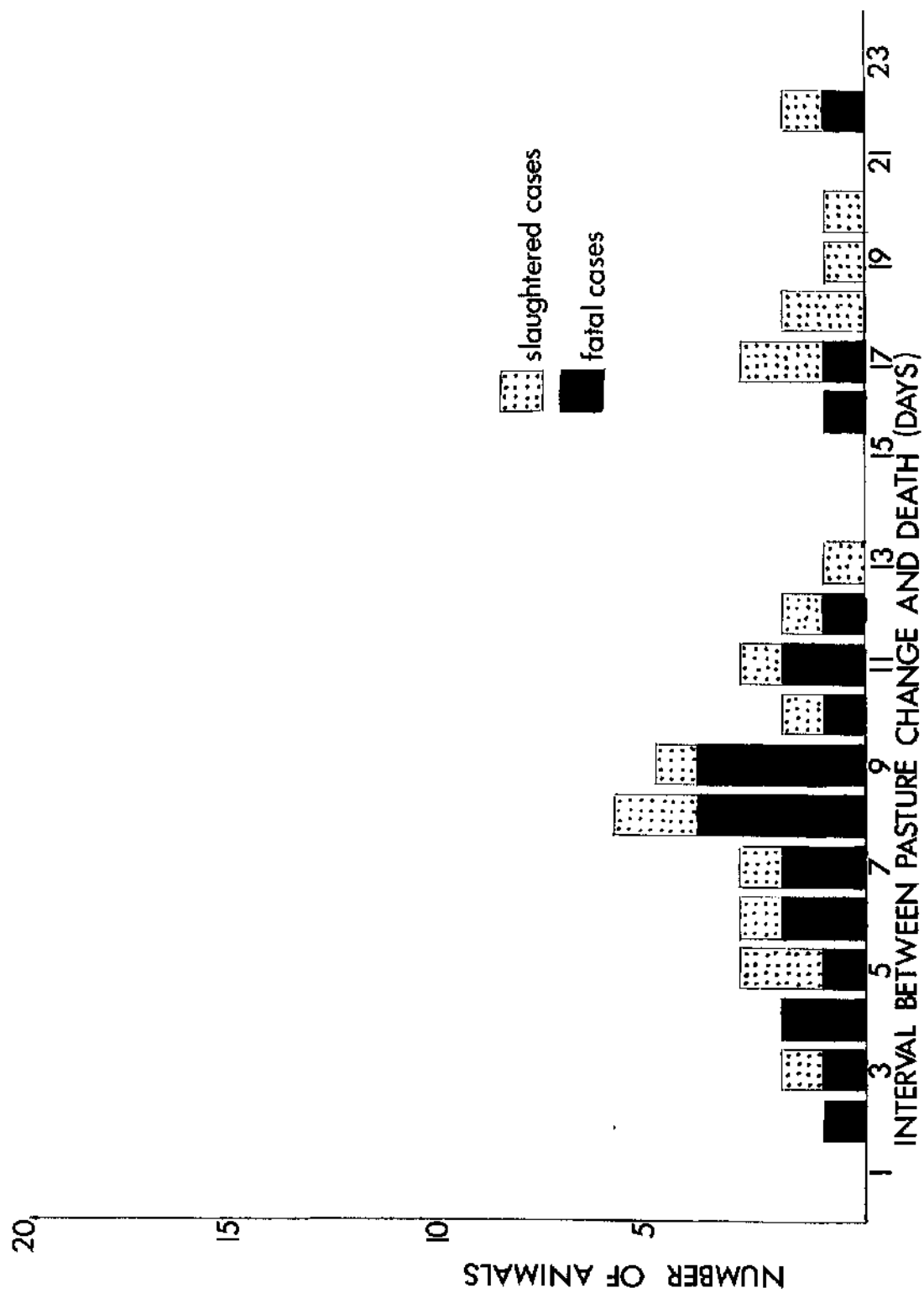


Fig. (6). Fog fever: time between first observation of clinical signs and death in 24 fatal cases.



(Fig. 7) Fog fever: Interval between last pasture change and death or slaughter in 43 cases.

THE PATHOLOGY OF FATAL CASES OF FOG FEVER.

The most significant pulmonary lesions in the fatal cases of fog fever have been set out in table (7). Detailed postmortem findings in each case are tabulated in Appendix (1). Macroscopic and histological observations in each case were very similar and the lesions differed only in degree; the animals have, therefore, been described as a group.

The macroscopic lesions in fatal cases of fog fever were confined to the respiratory system, the heart and the mediastinal and bronchial lymph nodes.

Larynx, trachea and bronchi

A very large number of petechial haemorrhages were found in the larynx, trachea and lobar bronchi (Figs. 8 & 9) and there was severe congestion of the lamina propria vessels; this gave a very deep red-purple colour to the lining of the airways. In a minority of animals, larger, focal haemorrhages were the source of a small volume of frank blood which lay free in distal segmental bronchi. Large haemorrhages were also found in the connective tissue dorsal to the larynx and between the cartilage rings of the trachea and bronchi (Fig. 9). There was oedema of the lamina propria of the larynx, trachea and bronchial tree; this was manifested as a slight thickening of this layer on macroscopic examination. Gross oedema of the larynx was never observed. White, frothy, pulmonary oedema fluid filled the lobar and segmental bronchi; this fluid was also found in the trachea and occasionally in the larynx or running from the nose. Very thin, clear mucus lay beneath the oedema fluid. Small greenish yellow mucous plugs were sometimes seen in small bronchi and in some instances there was focal bronchopneumonia;

these findings were inconsistent. The oedema fluid was seen in histological sections of the trachea and lobar bronchi as an eosinophilic, granular protein precipitate in the lumen. There was usually a light cellular exudation composed of macrophages, eosinophils and neutrophils in varying proportions. Since many of the animals had been dead for several hours at the time of examination, there were often many desquamated epithelial cells amongst these inflammatory cells. Migrating cells were found frequently between adjacent epithelial cells in the trachea and bronchi. Many of these cells were globule leucocytes; others were eosinophils, neutrophils or lymphocytes. Globule leucocytes were large cells and contained very many brightly eosinophilic, coarse granules; the cell nucleus was usually round, but sometimes was irregular when compressed between adjacent cells. The cytoplasm of the cell lay between the nucleus and the basement membrane when the globule leucocyte was found in the lower half of the epithelium or lay on the luminal side of the nucleus when the cell was in the upper part of the epithelium. The globule leucocytes in the bronchial epithelium stained similarly to the subepithelial mast cells with toluidine blue or astra blue/safranin and the coarse, acidophilic granules were larger and more discrete than those of eosinophils in H & E stained sections. Where the majority of epithelial cells were sloughed, as a result of postmortem changes, globule leucocytes could be found in the lumen also. Globule leucocytes were found in all cases in which the bronchial epithelium was well fixed. A small number of lymphocytes was consistently found in an intra-epithelial position (Fig. 10), but the number of eosinophils and neutrophils varied greatly. Some animals had an eosinophil infiltration of the lamina propria; in such cases eosinophils were often found intra-epithelially and in the lumen. Neutrophils were less frequently

seen and were usually confined to occasional bronchi containing a small volume of pus. The epithelium of the bronchial tree was often seen to be lifted away from the lamina propria, even in well preserved material and this appearance was considered to be the result of lamina proprial oedema, which could also be seen as separation of the connective tissue elements in most sections (Fig. 10). Intense congestion of the capillaries in the lamina propria, with many small haemorrhages, was found regularly. A number of mature plasma cells and cells of the lymphoid series was found in the lamina propria (Fig. 10), between the muscle bundles, around the bronchial mucous glands and in the peribronchial connective tissue. There were small aggregates of these cells, without the formation of germinal centres, in these sites in some animals. Eosinophils were found infrequently in these aggregates. Plasma and lymphoid cell accumulation in the peribronchial connective tissue was always heaviest in sections from the apical lobes, but germinal centres were not found.

Bronchioles A fine, eosinophilic, granular, protein precipitate was seen in most bronchioles (Fig. 11), sometimes this oedema fluid contained macrophages, neutrophils, eosinophils and occasional multinucleated giant cells (Fig. 12). The macrophages were large mononuclear cells; in many instances the nucleus was indented and phagocytosed material or cells could be observed in the cytoplasm; in others the cytoplasm was pale staining and vacuolated. Macrophages were usually the most numerous cell type (Fig. 12), but occasional bronchioles contained pus, free red blood corpuscles or a heavier eosinophil exudate. Small portions of eosinophilic or basophilic hyaline membranes were found alone or amongst the exudate in some bronchioles. Multinucleated giant cells often accompanied the

hyaline membrane pieces. Hyaline deposits, infiltrated by macrophages, were often seen to obstruct bronchioles and the distal parts of the bronchiole and its acini were then very overinflated. There was occasional bronchiolar epithelial hyperplasia and hyperchromatic nuclei or mitotic figures could be seen in some cases. Globule leucocytes were infrequently found in larger bronchioles. The lamina propria was oedematous and separation and lifting of the epithelium were common (Fig. 11); plasma cells, lymphoid cells and eosinophils were generally few in number but were regularly seen. The intensity of plasma and lymphoid cell infiltration of the peribronchiolar connective tissue varied greatly and aggregates of cells were frequent, especially in the apical lobes, but germinal centres had not developed (Fig. 12).

Respiratory acini and pulmonary parenchyma

The haemorrhage, congestion and oedema of the upper airways were always accompanied by severe congestion, interstitial emphysema and pulmonary oedema which involved the whole of both lungs.

The apical, cardiac, intermediate and ventral diaphragmatic lobes of both lungs were deep red or purple in colour, the result of intense pulmonary congestion (Fig. 14). Lobules in these lobes were very firm and rubbery on palpation and were not collapsed or depressed below the rest of the lung. After cross sectioning, the lobules were found to be markedly oedematous and congested; thin, blood tinged, oedema fluid ran from the cut surface. The sectioned lobules (Fig. 15) were red in colour and had a smooth, glassy, glistening appearance; pressure expelled more oedema fluid and gas bubbles. In a minority of animals, fine haemorrhages were found in some lobules.

Interstitial emphysema was severe and extensive in almost every case. Gas dissected along interlobular septa in all parts of the lung, but most dramatically in the diaphragmatic lobes (Figs. 15 & 16). There, the dorsal parts of the lobes were distorted by multiple, very large, interstitial bullae up to 15cm in diameter (Fig. 14). At the periphery of such large bullae, there were often deep purple, compressed, collapsed alveoli of adjacent lung segments. The interstitial gas was found in all parts of the lung, and occasionally in the mediastinum, the mediastinal lymph nodes (Fig. 17), the parietal pleura and peritoneum, at the thoracic inlet and subcutaneously in the neck and along the back. Gas was present in the perivascular and peribronchial connective tissue, and beneath the visceral pleura (Fig. 15). Almost all the enlargement of the diaphragmatic lobes was due to interstitial emphysema. Cross section of these lobes indicated that most lung lobules were similar to those of the rest of the lung, although some were very overinflated and less oedematous (Fig. 13). Segments of the dorsal parts of the apical and cardiac lobes were sometimes very overinflated and the portion of lung was then very spongy, but still deeply congested.

Pulmonary oedema was very severe, especially in the ventral half of the lungs, and yellowish, gelatinous oedema fluid was found extensively in the interlobular septa and perivascular connective tissue, accompanying the gas bullae (Fig. 15). The pulmonary oedema was the source of the large volume of frothy fluid in the bronchi and trachea. Thickened, oedematous interlobular septa could be distinguished in those segments not affected by interstitial emphysema. Subpleural oedema was common and oedema of the pleura produced an opacity of the surface of the lungs, most noticeable over the dorsal diaphragmatic lobes (Fig. 14). Dilated lymphatic

vessels were clearly visible, running beneath the surface of the thickened pleura. A small number of short, fibrous tags were found on the visceral pleura of the diaphragmatic lobes and were characteristically seen as a fringe along the caudal edge of the diaphragmatic lobes.

Examination of the lung revealed two types of lung lobule: one was very congested and oedematous with little overinflation of acini; the other was congested and very overinflated, with little oedema. These differences on gross inspection were confirmed on histological investigation.

Alveoli were filled by a fine, granular precipitate from the pulmonary oedema fluid (Fig. 18) and were usually lined by hyaline membranes. The hyaline membranes were often seen as eosinophilic strands, of varying thickness, on the epithelial surface of the alveolus, extending into the alveolar ducts and terminal bronchioles (Fig. 19). Sometimes hyaline material was present as a whorl or clump in the centre of the lumen (Fig. 20); in this position the material was occasionally surrounded by a ring of macrophages or infiltrated by these cells and multinucleated giant cells. Basophilic streaks were found in some hyaline membranes, especially those in the terminal bronchioles, and polymorphonuclear leucocytes, giant cells and macrophages were frequently enmeshed (Fig. 21). The hyaline membranes were strongly P.A.S. positive, both before and after diastase, were stained orange with P.T.A.H. and blue with picro-Mallory. The membranes did not differentiate with Gordon and Sweet's reticulin stain or with Weigert's elastin stain.

Basophilic streaked membranes in H+E sections were stained positively by the Feulgen method. Some clumped hyaline deposits in the alveoli stained red with picro-Mallory. Pulmonary oedema fluid was coloured pink with the P.A.S. reaction before and after diastase, orange with phosphotungstic acid haematoxylin and pale blue with picro-Mallory.

The extent of cellular exudation into the alveolar lumen was varied, though the cell types were similar in each case. Large mononuclear cells were the most frequent cell type. Most of these were alveolar macrophages (Fig. 22), characterised by their indented, bean shaped nuclei and abundant, eosinophilic cytoplasm, which contained phagocytosed material. This material was apparently derived from the pulmonary oedema fluid or the hyaline membranes and was seen as discrete eosinophilic, cytoplasmic inclusions, which stained positive with P.A.S., before and after diastase (Fig. 18). In other instances, phagocytosed polymorphonuclear leucocytes, eosinophils and occasional lymphocytes could be seen. Other macrophages contained several, large, clear vacuoles (Fig. 22), or red blood corpuscles which had been phagocytosed in areas of intra-alveolar haemorrhage. There were, however, other large mononuclear cells with large nuclei, often slightly indented, and pale, vacuolated cytoplasm (Fig. 23); these cells were similar to engorged macrophages and to the type 2 pneumocytes. Mitotic figures were occasionally seen in the large mononuclear cells in the lumen, in such instances the cytoplasm was generally more basophilic and inclusions were absent; the precise cell type could not be decided with the light microscope. Multinucleated giant cells (Fig. 24) were encountered in the alveolar spaces especially where hyaline membranes were prominent. Eosinophils were constantly found in the lumen, although the numbers varied from animal to animal and from field to field in the same lung section. An estimate of the extent of the alveolar and interstitial eosinophilia

was made in each case by counting the number of cells per high power (x 40) field. Neutrophils were constantly present, but varied in number; in a minority of animals, some acini and terminal bronchioles were filled with pus. Effete and dying cells were frequently seen in the alveolar spaces and all the cells of the exudate were represented in their number. Clear, pale staining portions of cytoplasm, which appeared to be membrane bound, were commonly found free in the lumen, without an associated nucleus. This material probably came from degenerating pneumonocytes or alveolar macrophages.

Alveolar epithelial hyperplasia was present in 21 of the 24 lungs examined, although the extent of the process was very varied in different parts of the same lung and in different animals. An estimate of the extent of this lesion was made using the grading system outlined previously and the result may be seen in table (7). In 3 animals the lesion was absent, although a large number of sections from all lung lobes were examined. In twelve instances the grading was 1+, in five, 2+ and in four, 3+. Where the grade was 1+, a minority of alveoli were found to be lined by short rows of low cuboidal cells (Figs. 25 & 26). These rows were usually 2-5 cells long and formed short ribbons, which were often separated from the underlying alveolar septum by a thin, clear space. The cuboidal cells had a round nucleus, with a single nucleolus, situated towards the base of the cell and a moderate amount of slightly basophilic cytoplasm which sometimes contained a variable number of clear vacuoles. This degree of change was present in the majority of alveoli of the lobule in grade 2+ (Fig. 27); the epithelial lining was complete in most alveoli of all lobules in grade 3+ (Fig. 38). In the latter case, the cells were more tightly packed and cuboidal, the apical cytoplasm was usually clearly vacuolated and quite basophilic. The epithelial cells rested on the alveolar septum when the tissue

preservation was good, but there were often many free large mononuclear cells in the lumen in grade 3+ lungs (Fig. 41). In grade 2+ or 3+ alveolar epithelial hyperplasia, the hyperplastic process was also found to extend into some alveolar ducts. Many of the hyperplastic alveolar epithelial cells were seen to have a pale staining apical cap of cytoplasm and this appeared to be the source of pale, cytoplasmic bodies in the lumen. Mitotic figures were frequent in the alveolar lining cells, (Fig. 42).

Some acini were grossly overinflated (Fig. 27) and in many instances the associated terminal bronchioles were obstructed by hyaline membrane plugs. There was often little cellular exudation or alveolar epithelial proliferation in such acini, although many were oedematous.

Alveolar septal capillaries (Fig. 25) were grossly congested in almost all the lungs examined; focal intra-alveolar haemorrhage was the major lesion in some acini. Eosinophils with a variable number of neutrophils were constantly present in the alveolar septa. In many cases it was clear that these cells were present in the septal capillaries, but it was also possible to distinguish them in the connective tissue.

In a minority of animals, some alveolar septa were found to be dilated so that a considerable space lay between the epithelial surfaces of adjacent alveoli (Figs. 22&23). This dilatation was the result of septal oedema. The dilated septa contained a slightly increased number of reticulin fibres and were stained very pale blue with picro-Mallory. Neutrophils and eosinophils were regularly present, as were larger mononuclear cells with elongated nuclei and indistinct cell borders. Plasma cells and lymphoid cells were very infrequently discovered in the alveolar septa.

Small, 0.5-1mm. diameter, aggregates of small lymphocytes with some plasma cells but without germinal centres were found at the periphery of a lobule, adjacent to the interlobular septum, in two animals. These aggregates were around terminal bronchioles.

The interlobular septa were very broad. Much of the enlargement was the result of tracking gas, but there was also oedema of the connective tissue and the lymphatic vessels were dilated and filled with granular, protein-rich fluid. There was also a cellular infiltration of the septa. Plasma cells and lymphocytes were always found, both in the connective tissue and in the lymphatics (Figs. 23 & 24). The numbers were varied and occasional aggregates of cells were noted. Neutrophils were frequent in some animals. Eosinophils were always present, either singly and frequently or in small aggregates (of up to 50 cells per high power field) in the connective tissue. Multinucleated giant cells were noted in the connective tissue and they were also found, sometimes in large numbers, with macrophages in the lymph vessels (Fig. 32). Plugs of clotted fibrin were observed periodically in these vessels.

Subpleural lymphatics were particularly dilated and the surrounding connective tissue was lightly infiltrated by plasma cells and lymphocytes. The pleural tags were found to be composed of connective tissue, mainly collagen.

Petechial and focal haemorrhages were present beneath the epicardium and endocardium of both ventricles of the heart and on the inner surface of the pericardium. Larger haemorrhages were noted at the base of the heart and in the connective tissue surrounding the proximal aorta, the pulmonary artery and the pulmonary veins. Lesions affecting the small pulmonary vessels, principally branches of the pulmonary vein, were constantly found. These lesions were present in all lungs, but

were more frequently seen in some animals. There was oedema of the connective tissue about both pulmonary arterioles and venules and gas bullae were frequently present. The walls of many pulmonary venules were swollen; the endothelium was lifted from the intima and the intima itself was pale staining and contained clear spaces (Fig. 28). There was often intense eosinophilic, hyaline staining of a segment of the media with loss of staining and increased translucency of an adjacent segment (Fig. 29). These changes were often particularly noticeable in the muscular prominences of the pulmonary venules. Eosinophils and neutrophils were sometimes seen in the lumina of the pulmonary arterioles and venules, in their walls and in the oedematous connective tissue about them; the numbers were always small (Fig. 39).

The mediastinal lymph nodes were always much enlarged, often to twice normal size. This was the result of marked oedema and the presence of a number of large gas bullae (Fig. 17). Congestion and severe haemorrhage were common findings and frank, clotted blood filled many gas bullae (Fig. 17). The bronchial lymph nodes were very rarely the site of gas bullae or haemorrhage.

The pulmonary lesions in fatal cases of fog fever have been set out in table (7) so that comparisons between the cases can be made. In the table (7) the duration of illness has been indicated. Only two dates in the history were likely to be accurate - the date of movement and the date of death. Precise knowledge of the time of onset of illness was not available since this depended on the illness being apparent to the farmer. The duration of illness has been stated from the time it was first noticed.

There was a particularly wide range of degree in the pulmonary lesions of the ten animals which died after an illness of one day or less in duration. Four animals were found to have marked interstitial

emphysema, oedema, hyaline membranes and early alveolar epithelial proliferation (1,2,9, & 10) and these might be expected to occur in this degree during the early stage of the disease. The other seven animals of this group were affected by more extensive alveolar epithelial hyperplasia and in three of these the lesion was diffuse. On theoretical grounds alone it is improbable that this pronounced hyperplastic lesion could develop in less than 24 hours. It is more likely that the duration of illness was not accurately known and the cases were not noticed early enough. Alveolar epithelial hyperplasia was very noticeable in non-fatal cases (see table 8) and the fatal outcome in these seven animals was almost certainly the result of the concurrent interstitial emphysema and pulmonary oedema. These latter two lesions were not found to the same degree in non-fatal cases.

The lung lesions of animals with an illness of up to two days duration were remarkably similar. Only one animal had more marked alveolar epithelial hyperplasia than the others and even this was not of the most severe degree: it was likely that this animal too had been ill for longer than two days (case 14).

Severe interstitial emphysema, pulmonary oedema and hyaline membranes were common to all the animals ill for at least 3 days. Five of the six animals in this group had alveolar epithelial hyperplasia of mild degree, and only one had the severe diffuse lesion; it is just possible that this could have developed in 3 days (vide inf.).

Both the animals which died on day 4 of their illness had similar degrees of pulmonary damage.

The major lesions in 15 of the 24 fatal cases were interstitial emphysema, pulmonary oedema and hyaline membranes and little or no alveolar epithelial hyperplasia. In nine of the 24 there was more extensive, concurrent, alveolar epithelial hyperplasia, which was

inexplicable in terms of the known duration of illness in eight cases. It is probable, therefore, that these animals had pulmonary disease for longer than the stated period, even if this had not been noticed by an untrained observer, the farmer. Animal 2 had been on the new pasture for four days; animal 3 for 21 days; 4 for 10 days; 5 for 10 days; 6 for 8 days; 8 for 15 days; 9 for 6 days; 11 for 7 days; 20 for 14 days. All had been on the new pasture for at least the period of 72-96 hours which is thought necessary for the development of diffuse alveolar epithelial hyperplasia.

ANIMAL	INTERSTITIAL EMPHYSEMA	PULMONARY OEDEMA	HYALINE MEMBRANES	EPITHELIAL HYPERPLASIA	PULMONARY EOSINOPHILIA	GLOBULE LEUCOCYTES	DURATION OF ILLNESS (DAYS)
1	+++	+++	++	+	moderate	frequent	1
2	+++	++	+	+	marked	frequent	1
3	++	++	++	+++	marked	occasional	1
4	+++	+++	++	+	moderate	occasional	3
5	+++	++	++	+	mild	occasional	3
6	+++	++	++	-	moderate	sloughed	2
7	+++	++	++	+	moderate	sloughed	3
8	+++	++	++	++	moderate	frequent	1
9	+++	++	+	+	moderate	frequent	1
10	+++	+	+	-	mild	sloughed	2
11	+++	++	++	+	mild	sloughed	3
12	+++	+	++	+	moderate	sloughed	2
13	+++	++	++	+	mild	occasional	2
14	+++	+++	++	++	marked	frequent	2
15	+++	++	++	++	moderate	frequent	1
16	+++	++	+	-	mild	occasional	2
17	+++	++	+	+	moderate	sloughed	3

(Cont. overleaf).

ANIMAL	INTERSTITIAL EMPHYSEMA	PULMONARY OEDEMA	HYALINE MEMBRANES	EPITHELIAL HYPERPLASIA	PULMONARY EOSINOPHILIA	GLOBULE LEUCOCYTES	DURATION OF ILLNESS (DAYS)
18	+++	++	++	+	moderate	frequent	4
19	(-)	(-)	+	+++	mild	sloughed	1
20	(+++)	(+++)	++	++	moderate	occasional	1
21	+++	++	++	+	mild	frequent	4
22	+++	++	++	++	moderate	frequent	1
23	+++	++	++	+++	moderate	sloughed	3
24	++	+	++	+++	marked	frequent	1

Table (7). The significant lesions in 24 fatal cases of fog fever.

THE PATHOLOGY OF NON-FATAL CASES OF FOG FEVER

Haemorrhages and congestion of the larynx, trachea and bronchi, which were striking features of fatal cases of fog fever, were absent in the slaughtered animals, although occasional petechiae were observed in the trachea and bronchi. Petechial haemorrhages on the epicardium and endocardium were also present less often; large haemorrhages at the base of the heart and about the extra-pulmonary portion of the pulmonary veins were noted in some animals. Pulmonary oedema was much less extensive and severe than in fatal cases and only a small volume of fluid could be expressed from the cut surface of the lung; this milder degree of oedema was reflected in the scanty volume of exudate in the trachea and bronchi and the lack of macroscopic submucosal oedema. Greenish-yellow mucous plugs blocked some smaller bronchi in a minority of cases and similar mucous strands were occasionally found in the trachea.

Interstitial emphysema was generally less marked or absent (Fig. 30), although in some cases there were severe, diffuse lesions. In this latter group, the typical lesions were overinflation of lobules in the apical and cardiac lobes, extensive gas tracking in the interlobular septa of all lobes and large bullae, up to 15cm. in diameter, in the diaphragmatic lobes (Fig. 31). Dissection of gas bullae followed the interlobular septa into the peribronchial and perivascular connective tissue (Fig. 31) and into the mediastinum and mediastinal lymph nodes. From the mediastinum, gas passed to the thoracic inlet, beneath the pleura or into the abdomen beneath the perirenal parietal peritoneum. A small number of thick, yellow, gelatinous oedema deposits accompanied these gas tracks in the interlobular septa and mediastinum. Gas infiltration outwith the lungs was

found in animals with moderate interstitial emphysema; in some animals with severe interstitial emphysema the lesion was confined to the lungs.

Pulmonary congestion was mild or absent and, in consequence, a widespread colour change was easily seen in the lung; this was the result of alveolar epithelial hyperplasia (Fig. 30, 31). Lobules affected by this lesion were typically fawn in colour, very firm or rubbery in consistency and not depressed below the remaining lung surface, except where adjacent lobules were puffy, white and overinflated. Cross section of fawn lobules (Fig. 31) revealed that the cut surface was smooth and glistening and that a little oedema fluid and a few gas bubbles could be expressed. The fawn, smooth, shiny appearance involved the entire lobule, although fine peripheral haemorrhages were occasionally seen. Alveolar epithelial hyperplasia was the most significant macroscopic lesion in many animals. The diffuse lesion involved the major proportion of all lung lobes (Fig. 30), but where it was localised it was almost always in the ventral parts. Fawn lobules were very heavy and rubbery and when this lesion was diffuse the weight of the lungs was greatly increased to 7-8kgm. In a minority of animals normal pale pink lobules were very difficult to find, since the alveolar epithelial hyperplasia was very diffuse (Fig. 30). Lobules not altered by alveolar epithelial hyperplasia were normal in appearance, with the exception of overinflated lobules (Fig. 30) or those in areas of collapse at the periphery of interstitial gas bullae (Fig. 31).

The visceral pleura was frequently found to be oedematous and the thickening produced opaque areas, generally over the posterior diaphragmatic lobes. Fibrous tags were noted in some lungs and were attached to the caudal edge or diaphragmatic surface of the diaphragmatic lobes.

Mediastinal lymph nodes were always greatly enlarged as a result of oedema and hyperplasia of the cortex (Fig. 17); gas bullae filled with blood were found in a minority of nodes. The bronchial lymph nodes were generally swollen to a lesser degree; haemorrhages and gas bullae were absent.

The histological findings in the bronchi and trachea were similar in nature to those of the fatal cases. A light cellular exudate, principally of macrophages with a smaller number of neutrophils and eosinophils, was found in the lumen amongst granular, eosinophilic, protein precipitate.

Globule leucocytes were very frequently found in the epithelium of the trachea and bronchi, in greater numbers than the acute cases (Fig. 33). The appearance of these cells was similar to that described previously. Migrating cells in an intra-epithelial position were regularly seen, often these were neutrophils or eosinophils but some lymphocytes were apparent. The epithelium was slightly lifted from the lamina propria in some sections and separated from loose connective tissue; since the tissue was otherwise well fixed this was attributed to oedema of the lamina propria. (Fig. 33). Congestion of the blood vessels of the lamina propria was not common. There was a variable but constant infiltration of the lamina propria by plasma cells and lymphocytes (Fig. 33). Small aggregates of lymphocytes and plasma cells, without germinal centres, were present in most animals in the lamina propria, and in the peribronchial connective tissue. Small numbers of plasma cells and lymphocytes usually surrounded the submucosal glands and the muscle layer. A few neutrophils and eosinophils, in small or moderate numbers, were constantly found in the lamina propria.

Some small bronchi and bronchioles were filled by large numbers of macrophages, portions of hyaline membranes and small

numbers of eosinophils, multinucleated giant cells and neutrophils. Mucous plugs infiltrated by macrophages and a few eosinophils were found in a minority of cases. Terminal bronchioles and alveolar ducts often contained thick hyaline membranes arranged linearly or in clumps. Macrophages containing P.A.S. positive material in their cytoplasm and multinucleated giant cells were often found in and around the hyaline material and clumped deposits were usually ringed by these cells. Both eosinophilic and basophilic streaked hyaline membranes were found, the latter more frequently in the bronchioles and alveolar ducts. There was swelling and oedema of the lamina propria of the bronchioles and mitotic figures were sometimes noted in hyperplastic epithelium. Globule leucocytes were not present in the bronchioles. In some animals the muscle coat of small bronchi and bronchioles was found to be hypertrophied. Peribronchial lymphoid infiltration and aggregation was continued to a lesser degree in the peribronchiolar connective tissue. The lymphoid infiltration at all levels was usually most marked in the apical lobes.

Alveolar oedema was present to a minor degree in most lungs. Oedema and hyaline membranes were the only lesions in some alveoli but they were found more commonly in association with alveolar epithelial hyperplasia. Hyaline membranes and deposits were present in many alveoli and were well developed, either lining the alveolar walls or forming whorled deposits in the lumen (Fig. 34). Many macrophages and giant cells infiltrated the membranes and deposits in most alveoli (Fig. 34). The deposits in the lumen were often surrounded by a ring of macrophages (Fig. 34). Some deposits were very basophilic and irregularly whorled.

In picro-Mallory stained sections, some hyaline deposits were stained, red especially where the deposits appeared to be organising (Figs. 36, 37). Alveolar epithelial hyperplasia was the most significant lesion in most animals and in the majority of lung sections examined, from all lobes, almost all the alveoli were affected (Figs. 38, 40). In some sections, alveolar epithelial hyperplasia extended over half a lobule: the other half was overinflated and contained foci of oedema and hyaline membranes. The alveoli were lined by a single layer of cuboidal cells which also extended into the alveolar ducts (Fig. 41). Large numbers of similar cells, (often 20 or 30) could be found free in the alveolar spaces, where they tended to form aggregates (Fig. 41). The cuboidal lining cells were frequently found to contain mitotic figures (up to 4 per H.P. field) and the nuclei were usually hyperchromatic (Fig. 42). Sometimes there was only a small amount of basophilic apical cytoplasm but in other cases this was more abundant and very vacuolated (Fig. 42). These vacuoles did not stain with any of the techniques employed; in Toluidine blue stained 1 micron thick sections additional small, dark granules were also noted in the cytoplasm of a few cells on the alveolar wall and in the cytoplasm of free cells in the alveolar spaces (Fig. 22^{110x}). In some epithelial cells, the apical cytoplasm was thrown into an irregular pale staining 'cap' and small, round portions of similar material were seen in the lumen (Fig. 42). A very extreme degree of alveolar epithelial hyperplasia was observed in some animals: in these the alveoli were lined and filled by cells apparently derived from the epithelium (Fig. 35). The cytoplasm of some of these cells contained P.A.S. positive, diastase-resistant material; similar material was found in alveolar macrophages and this could have been derived from hyaline membranes (Fig. 35).

Free cells in the lumen were similar to the cuboidal epithelial cells and to the alveolar macrophages. Not all the cell nuclei were indented, however, and phagosomes or ingested cells were not apparent. The cells forming the alveolar epithelium and a proportion of the free cells were cytologically identified, as type 2 pneumonocytes, in a later section of this study.

Eosinophils were present in the alveoli and alveolar septa in varying, usually moderate numbers (Figures 44 and 45). Neutrophils and mast cells were less frequent and plasma cells and lymphocytes very rarely observed. Alveolar septa were frequently very dilated (Fig. 43) and contained elongated large mononuclear interstitial cells, a few neutrophils and a moderate number of eosinophils (Fig. 43). This thickening was mostly the result of oedema of the septum, with a very small increase in the reticulin content. Some alveolar septa were stained pale blue with picro-Mallory as a result of the oedema (Fig. 36). Fine collagen fibres were apparent focally, but there was no fibrosis and no infiltration of plasma cells or lymphocytes. The large mononuclear interstitial cells were elongated, with spindle shaped, pale staining nuclei and indistinct cell borders (Figs. 42, 43). Most of these cells were in the interstitium (Figs. 36, 43). A few rounded, but otherwise similar, cells were probably monocytes in the septal capillaries. Mitotic figures were noted very occasionally in the alveolar septa, apparently in the interstitial cells. The alveolar septa were occasionally exceptionally dilated and the connective tissue was very oedematous. In three animals there were focal lesions in which resolving intra-alveolar exudates, including hyaline membrane material, appeared to have been incorporated into the alveolar septa; here there were slightly more collagen fibres (Fig. 37).

Aggregates of lymphocytes and plasma cells, without germinal centres, were found singly at the periphery of some lobules and in the interlobular septa. Eosinophils were frequently numerous and gathered into aggregates in the interlobular connective tissue and lymphatics. Multinucleated giant cells, macrophages and neutrophils were regularly found in the interlobular lymphatic vessels and in the connective tissue about them. A constant plasma cell and lymphocyte infiltration and aggregation was also present. Oedema of the connective tissue and gas bullae in the lymphatics were frequent. Plugs of fibrin filled some lymphatics.

The pleura was often oedematous and eosinophils, plasma cells, lymphocytes, macrophages, multinucleated giant cells and some neutrophils were found in the subpleural lymphatics.

The lesions in the lungs of each case are summarised in table (8) and in more detail in appendix (1).

One animal (25) was killed after a fairly mild illness of 1 day in duration. The herd had been affected by fog fever in the previous year, when one cow died and was examined by us. This year, the farmer was apprehensive; he removed the animals from aftermath at the first sign of increased respiratory rate and sold this one (25) to us.

Four animals (26,27,32 & 35) had been ill apparently for 2 days. The extent of alveolar epithelial hyperplasia suggested that the period of illness was longer than this.

Two animals (28 and 34) were slaughtered on the third day of their illness. Number (28) was another mild case, like (25). The owner was only willing to sell this cow, because she was not in calf. The alveolar epithelial hyperplasia in (34) could have developed in 3 days.

Nine animals (29,30,31,33,36,37,38,39,40) were ill for 4-7 days. Three of these (31,38, and 40) did not have extensive alveolar epithelial hyperplasia, although the known period of abnormality appeared to have

been long enough for this to have developed.

Numbers (41), (42) and (43) were mild cases in which there was a relatively long interval between movement and death.

CASE	INTERSTITIAL EMPHYSEMA	PULMONARY OEDEMA	HYALINE MEMBRANES	ALVEOLAR EPITHELIAL HYPERPLASIA	PULMONARY EOSINOPHILIA	GLOBULE LEUCOCYTES (BRONCHI)	DURATION OF ILLNESS (DAYS)
25	+	+	+	-	moderate	many	1
26	+++	+	-	+++	moderate	many	2
27	++	-	-	+++	light	many	2
28	+	-	-	focal	light	many	3
29	++	+	-	+++	light	many	5
30	+++	+	-	++	moderate	many	5
31	++	+	+	+	moderate	many	6
32	++	-	-	+++	moderate	many	2
33	++	+	+	+++	light	many	6
34	+++	+	-	+++	light	many	3
35	++	+	+	+++	light	many	2
36	+	+	-	++	light	many	7
37	+++	-	-	++	light	many	6
38	+	-	-	focal	moderate	many	7
39	++	-	-	++	light	many	4
40	+++	+	+	focal +	light	many	4
41	++	-	-	-	moderate	many	17
42	+	-	-	-	very light	many	8
43	+	-	-	focal +	very light	many	9

Table (8) Fog fever: significant pulmonary lesions in 19 non-fatal cases.

Lesions in other organs in fatal and non-fatal cases of fog fever

LIVER Both fatal and non-fatal cases were found to have liver lesions as a result of infection or reinfection with Fasciola hepatica; almost all animals were affected. All of the fatal cases were observed to have passive congestion and fatty change of the liver, but there were no instances of frank hepatic necrosis.

ABOMASUM Numerous nodules were noted in the wall of the abomasum of most animals and were the result of Ostertagia infections; none were associated with signs of clinical disease.

ALIMENTARY SYSTEM Traumatic reticulitis was an incidental observation in one animal. Three fatal cases had eaten leaves; this was considered to be a sign of pasture shortage before movement.

HEART Sarcocysts were observed in histological sections from the cardiac muscle of many animals.

KIDNEY Incidental lesions were focal pyelonephritis or interstitial scars of mild degree in a few cases.

BACTERIOLOGICAL FINDINGS IN THE LUNGS OF FATAL AND NON-FATAL CASES

The results of bacteriological examinations of the lungs and bronchial tree in the fatal and non-fatal cases have been set out in tables (9 and 10).

There were no significant observations.

PARASITOLOGICAL FINDINGS IN THE LUNGS OF FATAL AND NON-FATAL CASES

The results of Baermann examinations of the lungs of 10 fatal cases and 9 non-fatal cases have been given in table (11). Twenty lungworm larvae were recovered from the lungs of one fatal case (No 16). Two larvae were found in the sample from one non-fatal case (26) and one adult lungworm was observed in a bronchus in histological sections from animal 31, although no lungworms had been recovered after the Baermann examination.

ANIMAL	ORGANISMS RECOVERED FROM LUNGS AND BRONCHI
1	N.S.F. (no significant findings)
2	N.S.F.
3	Haemolytic <u>Streptococci</u> and <u>E. coli.</u>
4	N.S.F.
5	N.S.F.
6	N.S.F.
7	N.S.F.
8	<u>E. coli.</u>
9	N.S.F.
10	<u>E. coli.</u>
11	<u>E.coli.</u>
12	N.S.F.
13	<u>E. coli.</u>
14	<u>E. coli.</u> , and <u>Proteus</u>
15	Autoagglutinable <u>Salmonella</u> -like coliforms
16	N.S.F.
17	<u>E. coli.</u>
18	N.S.F.
19	Not done
20	Not done
21	N.S.F.
22	<u>E. coli.</u> , Gram negative cocci, yeasts
23	N.S.F.
24	N.S.F.

Table (9). Fog fever: bacteriological findings in the lungs
of 24 fatal cases.

ANIMAL	ORGANISMS RECOVERED FROM LUNGS AND BRONCHI
25	N.S.F. (no significant findings)
26	Non-haemolytic Streptococci
27	Pasteurella-like organisms
28	N.S.F.
29	E. coli. and Proteus
30	N.S.F.
31	N.S.F.
32	N.S.F.
33	N.S.F.
34	Non-haemolytic Streptococci
35	N.S.F.
36	N.S.F.
37	Haemolytic Streptococci
38	N.S.F.
39	Haemolytic Streptococci (Group C)
40	<u>Actinomyces graminis</u>
41	N.S.F.
42	N.S.F.
43	N.S.F.

Table (10). Fog fever: bacteriological findings in 19 non-fatal cases.

ANIMAL	DICTYOCAULUS VIVIPARUS RECOVERED FROM LUNGS
1	NONE
2	NONE
3	NONE
4	NONE
5	NONE
7	NONE
12	NONE
15	NONE
16	20 larvae
24	NONE
25	NONE
26	2 larvae
29	NONE
31	NONE *
32	NONE
34	NONE
36	NONE
40	NONE
41	NONE

* one adult lungworm was observed in histological sections from the lungs of this animal.

Table (11). Results of Baermann examinations of the lungs of 19 animals affected by fog fever.

DOUBLE DIFFUSION TESTS FOR PRECIPITATING ANTIBODIES TO M. FAENI

The results of the double diffusion tests for precipitating antibodies to M. faeni have been given in table (12). Many of the fatal cases died before blood samples could be obtained and these were included in the 'not tested' category. No precipitating antibodies were detected in any sera from fatal and non-fatal cases.

PRECIPITATING ANTIBODIES TO <u>MICROPOLYSPORA FAENI</u> IN THE SERUM	NUMBER OF ANIMALS
PRESENT	0
ABSENT	30
NOT TESTED	20

Table (12).

Fog fever: precipitating antibodies to
Micropolyspora faeni in the sera of 50 cases.

DISCUSSION

Although fog fever has often been compared to diseases of cattle in other countries and has been described as a pulmonary disorder of cattle in Britain on many occasions, there are no complete descriptions of actual cases of the disease in the literature. In particular, there is no series of cases in which the clinical signs, epidemiology and pathology have been detailed. This lack of definitive description of the syndrome has led to most of the confusion in the literature, to the concept of a multiple aetiology of the syndrome and to several unfounded associations based on misunderstandings, particularly with regard to farmer's lung of man.

The present study is the first/^{extensive} clinico-pathological investigation of fog fever and other respiratory diseases of adult cattle in Britain. Certain aspects of the clinical and epidemiological observations in our field survey were pertinent to the definition of fog fever and these have been discussed below: the results and discussion of these topics are set out and expanded more fully elsewhere (Selman et al - to be published).

Our investigation of 50 cases of fog fever, obtained from 30 incidents of the disease, indicated that fog fever was an acute onset, respiratory distress condition in adult beef-type cows, that developed soon after a change of pasture to better grazing in the autumn.

Clinical cases were found from late August to November and the disease was first manifested between one and fifteen days after the pasture change. Fatal cases generally succumbed during the first four days of illness. The main pulmonary lesions associated with the

disease were interstitial emphysema, pulmonary oedema and hyaline membranes and proliferation of the type 2 pneumonocytes.

Most incidents of the disease were first noticed when one or more cows was found to be severely ill or died suddenly. Examination of the herd at this time, by an experienced clinician, indicated that many other animals exhibited a lesser degree of clinical signs, which were either unappreciated by the owner or not sufficiently alarming to give him cause for concern. Although the morbidity was high, the mortality was low and the farmers recognised that the condition was unlikely to be fatal in milder instances.

Most of the 50 animals were mature adults, aged from 4-9 years, a few were older than this and the youngest was an in-calf heifer of 2-3 years. All these animals were older than those found to be affected by post-patent husk in our field survey.

Only females were affected. This apparent sex susceptibility may be fortuitous rather than genetic, since it was not the practice to keep herds of adult males outdoors under the same system of management.

Several beef breeds were represented in the 30 incidents; these breeds formed the predominant types in the herds in the districts. Two Friesian animals examined were managed under a beef cow-suckler calf system, as were all the other cases of fog fever. This system of management seemed more important than the actual breed; dairy-type cattle were affected in beef herds, but we never encountered fog fever in milking cows. The term "beef-type" was used to embrace all breeds of cattle under suckler cow husbandry. In practice Herefords and their crosses predominated, but this type was particularly common in most herds. The apparent susceptibility

of the Hereford breed has been noted by many others, but this has never been evaluated statistically.

All 30 incidents occurred in the period from the last week of August to the end of November. There was a definite seasonal incidence in the autumn months, although the precise period varied from year to year.

Every animal became ill after a move to fresh pasture, the time between the last movement and first appreciation of clinical signs varied from 1-21 days. Since the time period was based on the farmer's recollections, the accuracy depended on him. The latter figure of 21 days was probably incorrect and most cases developed within 15 days of the pasture change.

The duration of the subsequent illness depended on the course during the first 4 days after signs were noticed. The fatal cases all died within this period. The non-fatal cases had been ill for 1-17 days, although most had been ill between 1 and 9 days. The clinical signs in 15 of the 19 non-fatal cases were not considered to be severe enough to cause death and most cows appeared to be recovering at the time of slaughter. A number of fatal cases dropped dead in transit or whilst walking to the farm; some of these may have recovered without these stresses. One cow (No 35) was slaughtered, in extremis, on humane grounds.

The nature of the new grazing was varied, in many cases it was aftermath, in others permanent grass or rape. Always there was more and better herbage on the new field than on the previous one. If the fresh grazing had received one or two dressings of nitrogenous fertiliser earlier in the season, the quality of the grass reflected this. The move from a low plane of nutrition to a higher one seemed to have a bearing on the development of the disease

but the nature of the fresh pasture, i.e. whether it was aftermath or permanent grass, was less important, provided it was well grown.

Many of the cows had calves at foot: none of these younger animals ever exhibited the severe signs of fog fever, although a number were tachypnoeic and coughing. Faecal samples from the calves revealed the presence of 50-100 lungworm larvae per gramme in some cases.

Two animals were said to have been affected by fog fever previously. This information was provided by the owner or his veterinary surgeon. We were not able to verify this assertion. Despite the low occurrence of repeated affection in any particular cow, incidents were encountered on the same farms in different years.

Our field investigation has indicated the main clinical and epidemiological features of fog fever. Our results are generally in agreement with the clinical reports of earlier investigators, although we are able to be more categorical and specific about certain points. The broader enquiry into the respiratory diseases of adult cattle made it clear that the fog fever syndrome could only be interpreted after considering all the causes of respiratory distress in adults.

Fog fever, as I have defined it, is a disease which affects beef-type cattle. Barker (1948) and Leslie (1949) mentioned that beef cows developed fog fever but both authors made particular note of the disease in dairy cows. These became ill when being brought in for milking and such cases frequently terminated fatally. Begg and Whiteford (1948) opened their paper with the remark that the disease they were describing was "an enzootic affecting milk cows at pasture" and they did not include beef cows in their discussion. Once more they stressed that the condition was "invariably

noticed when the milk cows are brought in for the morning milking". Although Begg and Whiteford are often credited with describing fog fever, they did in fact refer to their syndrome as "Acute Interstitial Pulmonary Emphysema" of bovines and the association with fog fever was made later (Maclean 1949). In my opinion, Begg and Whiteford did not record fog fever in this paper.

Roberts et al (1973) conducted a survey into fog fever in Wales and their results were claimed to represent over 800 cases of the disease. They were not able to discover if there was a higher incidence in beef cattle compared to dairy animals. They considered fog fever to be a disease of "cows", of which "beef cattle were the usual victims" but did not provide any figures to support this claim. Their conclusion that breed and type were immaterial was said to be supported by the work of Barker (1948), Leslie (1949) and Begg and Whiteford (1948). This is not so.

A working definition of fog fever is given in the third paragraph above. We did not encounter fog fever as a disease of milking cows, according to the above criteria, nor are there satisfactory descriptions in the literature. It may be that cases could develop when milking cows are moved from a very poor pasture to a richer grazing, but the more usual practice is to keep milk cows on a constant high plane of nutrition. Although the possibility of incidents in milk cows cannot be totally ruled out, there is no fully documented outbreak recorded in the literature.

The acute respiratory signs described by Barker (1948) and Leslie (1949) in adult beef cows are comparable to fog fever as we know it. The sudden respiratory distress in adult dairy cows, reported by Barker (1948), Begg and Whiteford (1948) and Leslie (1949), is remarkably similar to that in the two cases of acute pulmonary oedema and

interstitial emphysema which were examined by us. Our findings from these two cases indicate that there may be a syndrome in dairy cows which is comparable to "milk allergy" described by others (Campbell 1970 a & b). This is wrongly called 'fog fever', since there are clinical, epidemiological and pathological differences from this disease. Further investigation is required to confirm this view.

Roberts et al claimed that "the clinical and circumstantial features" of fog fever in Wales "correspond well to those observed by Begg and Whiteford" in Scotland. Roberts et al described a disease affecting mainly beef cattle; Begg and Whiteford specified a disease of dairy cattle "invariably noticed when the milk cows are brought in for the morning milking". This is a fundamental difference: Roberts et al did not mention this latter syndrome at all.

All that can be said of the sparse, incomplete, clinical literature available is that there are acute respiratory syndromes in beef and dairy cows. The reports of Barker (1948), Begg and Whiteford (1948) and Leslie (1949) can be interpreted to support the view that these are different epidemiologically and, possibly, have different aetiologies.

Fog fever was found to be a disease of adults by Barker (1948) and Leslie (1949), although the calves at foot were not ill. This agrees with our results. Barker also referred to animals developing fog fever in their first grazing season and noted that coughing was a feature of the disease. Coughing was not considered to be a major sign by Leslie (1949) and was not common in the cases we examined. Coughing is a cardinal sign of parasitic bronchitis, but the clinical and pathological features of this disease were not clarified until after Barker's paper (Jarrett et al 1954 and 1957). All grazing animals under 2 years old in our survey were found to

have parasitic bronchitis and it seems likely that these young animals noticed by Barker were affected by the same disease.

Most authors agreed that the autumn months contained all the cases. Leslie (1949) claimed September to November, largely the same period as ourselves; Barker (1948) July to November. Roberts et al (1973) stated July to December, but did not provide details of the outbreaks which would enable further analysis to rule out parasitic bronchitis. It is noteworthy that our field outbreaks of parasitic bronchitis began in July and August, that is slightly earlier than the fog fever incidents.

All our cases were associated with a recent change of pasture, generally in the previous 15 days. Barker (1948) noted that the main period was 10-12 days after the change and Leslie (1949) found a proportion of cases in the first few days. Roberts et al (1973) acknowledged that most practitioners recognised the danger period to be 3-10 days after a change to better grazing, but, surprisingly, came to the conclusion that there was no definite association with pasture change and that the "British experience is more towards the sporadic occurrence of cases over a period". These authors may have been misled by farmers' recollections of dates, since their interviews were 'a few weeks' after the initial diagnosis. Their claim that cases developed without pasture change was based on incidents on bare fields continuously grazed (this is also mentioned by Leslie). Before accepting this statement, one would require postmortem evidence of the pulmonary lesions and an adequate consideration of other respiratory disorders in a differential diagnosis. They stated that "other forms of pneumonia were differentiated by temperatures over 104°F. while parasitic bronchitis was suspected on grounds of history, age and opportunity of exposure": this is succinct but

hardly persuasive. Only 4 animals were examined at postmortem in that survey of over 800 alleged cases. In our survey, only one third of the cases submitted proved to have fog fever. All incidents on bare fields and without a history of movement were found to be the result of parasitic bronchitis.

We found a clear association between the development of clinical signs and movement of beef cows and suckler calves from quite bare pastures to much better grazing. Barker (1948) remarked on fog fever's relationship to foggage, a richer grazing, but did not comment on the previous pastures. Leslie (1949) observed that the farmers blamed fertilisers and reseeded (which presumably produced lush grass), but did not elaborate further. Roberts et al (1973) noted respiratory disease occurred in cattle on different types of grazing.

The published literature in Britain to date is broadly in agreement with the results of our survey. There are inconsistencies, but these can be attributed to lack of sufficient clinical, epidemiological or pathological data in the original reports.

The pathology of fog fever has never been systematically defined from necropsy studies of actual clinical cases. The 50 cases examined in this study can be considered under the following groups-

- the most severely affected animals which died within 4 days of the first clinical signs (24 cases).
- less severely ill animals which would have recovered but were slaughtered to study the pulmonary lesions (19 cases).
- animals which were allowed to recover and which were slaughtered when clinically normal (7 cases).

The fatal cases were characterised by severe pulmonary and bronchial congestion, marked petechiation of the trachea and bronchi; very

severe interstitial emphysema; severe pulmonary oedema and hyaline membranes and early proliferation of alveolar epithelial cells.

The non-fatal cases were found to have less interstitial emphysema and oedema and little haemorrhage into the bronchial tree, but more diffuse, severe alveolar epithelial hyperplasia, the result of type 2 cell proliferation.

The seven cases examined much later did not have any of these lesions.

These findings suggested a sequence of lung lesions beginning with interstitial emphysema, pulmonary oedema and congestion with hyaline membranes and the multiplication of type 2 pneumonocytes becoming apparent soon afterwards. This combination of interstitial emphysema and pulmonary oedema often proved fatal in the first 4 days. Less extensive interstitial emphysema and oedema were noted in those animals surviving this period but the proliferative response in the alveoli was often very marked, indicating that about 72-96 hours was required for this pulmonary lesion to develop. Pulmonary oedema had possibly been resolved in these animals. Although extensive alveolar epithelial hyperplasia was found in fatal cases, the lesion could clearly regress, since most of the non-fatal cases were apparently recovering. There was no evidence that marked, residual, alveolar septal fibrosis or alveolar epithelial hyperplasia was present in the seven recovered cases.

The similar clinical histories and the comparable pulmonary lesions, which differed mainly in degree, were consistent with the fatal and non-fatal cases being examples of the same disease process. Fog fever can be considered to be -

- a sudden severe illness terminating fatally within a few days
- a severe illness which abates slowly and from which the animal

might recover, if it survives the first 4 days and, probably,
- a mild disease obvious to the experienced
clinician, but not of concern to the farmer.

All these three grades of the illness were apparent in each disease outbreak and animals affected by predominantly interstitial emphysema and pulmonary oedema or by extensive alveolar epithelial hyperplasia were found together in the same incident. This is consistent with the view that fog fever is one syndrome in beef animals.

The main pulmonary lesions in fog fever are interstitial emphysema, pulmonary oedema and hyaline membranes and alveolar epithelial hyperplasia of type 2 pneumonocytes. These changes are not pathognomonic of fog fever - which can only be defined in the form of a clinical, epidemiological and pathological entity. The pulmonary pathology of the cases of fog fever described in this report is comparable to that mentioned by Mackenzie (1965 and 1966). Hepatic necrosis and degenerative changes in hypertrophied pulmonary arterioles were noted in fog fever by Mackenzie but were not found in the cases described above. It is not possible to say, from the published work, whether the cases detailed by Mackenzie were all consistent with a diagnosis of fog fever based on our criteria. In this survey, degenerative changes were found in pulmonary venules and these were especially noticeable in the muscular prominences; this may have been the reaction mentioned and attributed to arterioles by Mackenzie.

It is very probable that the sequence of events in fog fever is : initially pulmonary oedema and congestion, closely followed by interstitial emphysema, then by hyaline membrane formation and finally alveolar epithelial proliferation. The stimulus to all these changes might be applied at the same moment.

The bovine lung is particularly susceptible to the formation of interstitial emphysema because there is marked lobulation of the lung and the interlobular connective tissue is very loose. Once gas has entered the interlobular septum, it can easily travel along the interstitial tissue planes. Furthermore, it has been postulated that the respiratory bronchioles of the cow curve to lie adjacent to the interlobular septa, in such a way that rupture of the bronchiole enables gas to enter the septa without difficulty (Jarrett 1956). Once interstitial emphysema is initiated, it may extend along loose tissue planes during the course of respiratory movements, especially those heightened by dyspnoea. The manner in which the lesion commences is less obvious. There is no indication that interstitial emphysema in fog fever is an extension of a longstanding, destructive process comparable to centrilobular or pan-acinar emphysema of man; the gross overinflation of acini in fog fever appears to be an acute lesion. Production of emphysema is often attributed to the "ball-valve" effect of intra-bronchial obstructions which, in the case of fog fever, could be provided by the aggregates of inflammatory cells and condensed hyaline material frequently found in small bronchioles. However, severe interstitial emphysema may be found, with pulmonary oedema, before such obstructions are noted, which suggests that blockage is not the cause. Interstitial emphysema may be seen in animals which have been humanely slaughtered and, though the lesion is rarely extensive, it can clearly be begun, without underlying pathology, by a raised intra-alveolar pressure, probably due to expiratory efforts against a closed larynx in this instance.

It is hypothesised that in fog fever, the interstitial emphysema is the result of bronchospasm, possibly exaggerated by dyspnoea due to pulmonary oedema. Laryngospasm might also be involved. There would be increased intra-alveolar pressure on expiration when bronchospasm was present and the effects of this would be heightened by the increased respiratory efforts caused by concurrent pulmonary oedema. Elevated pressure in the acini on expiration would lead to rupture and release of gas into interstitial tissues.

Bronchospasm, the result of contraction of the smooth muscle coat, could be induced by mast cell discharge as in bronchial asthma of man (Crofton and Douglas 1969). The presence of globule leucocytes in large numbers in the bronchial epithelium of cases of fog fever indicates that mast cell discharge in the lamina propria has taken place previously. It is not possible to place a time-scale on this since the period globule leucocytes persist in the bronchial tree of cattle is unknown. These intra-epithelial globule leucocytes may have no bearing on muscle contraction, this may be the function of the mast cells which are found in the bronchial muscle: discharged mast cells in muscle could be demonstrated by the Falck technique (Falck et al 1964). Oedema of the lamina propria of the bronchi and possibly the petechial haemorrhages and congestion could be the result of local mast cell discharge. Swelling of the mucous membrane would narrow the airway further. If globule leucocytes can be an indicator of bronchospasm, then this process might also be responsible for some of the clinical signs in reinfection husk, in which intra-epithelial globule leucocytes are very frequent. Interstitial emphysema is not a prominent lesion in reinfection husk but this may be because bronchospasm must be compounded by another lesion, such as pulmonary oedema, before interstitial emphysema can be initiated.

There is experimental and anatomical evidence to support the hypothesis that pulmonary oedema is a primary lesion in fog fever and that this oedema is the result of pulmonary vein constriction.

The pulmonary vein of cattle has a well developed muscle coat (Alexander and Jensen 1963) and the vessel is well supplied by nerves and mast cells at certain points (Hebb 1969). The pulmonary vein is considered to be a primary target tissue in bovine anaphylaxis (Eyre 1971a; Wells et al 1973). It might be expected that constriction of the pulmonary vein would produce an acute rise in hydrostatic pressure in the capillary bed of the lung and this would result in severe congestion and pulmonary oedema, especially if right ventricular output was maintained. Experimental results verify this. Aitken and Sanford (1969a) subjected calves to anaphylactic shock and found that a brief period of apnoea was followed by marked systemic arterial hypotension with pulmonary arterial and abdominal venous hypertension. This was accompanied by pulmonary oedema, congestion and interstitial emphysema. Eyre et al (1973) extended this work and observed that pre-treatment of the animals with sodium meclofenamate or a combination of diethylcarbamazine citrate and disodium cromoglycate given at the time of challenge could suppress the cardio-pulmonary changes of anaphylaxis. Eyre (1971a) investigated Schultz-Dale reactions in bovine pulmonary vein in vitro and found that these reactions might be inhibited by sodium meclofenamate (an antagonist of kinins and slow-reacting substance, SRS-A) or by a mixture of disodium cromoglycate (an inhibitor of type 1 hypersensitivity) and diethylcarbamazine citrate (an SRS-A antagonist). Wells et al (1973) concluded that pulmonary vein contraction could be the result of an intrinsic local response in the smooth muscle of the vein, or mediated by substances in the blood released as a result of antibody-antigen interaction in

pulmonary or other tissues. The pharmacologically active substances believed to be released in bovine anaphylaxis include histamine, serotonin, dopamine, kinins, slow reacting substance (SRS-A) and possibly prostaglandins and "rabbit cortex contracting substance" (Aitken and Sanford 1969b; Eyre 1971b, 1972a; Eyre and Lewis 1972; Wells and Eyre 1972; Eyre et al 1973). The presence of such substances in the circulation might be expected to intensify the oedema by action on the capillary bed of the lungs. Majno et al (1967) observed that histamine, serotonin and bradykinin had a direct effect on capillary endothelium, which was induced to contract, resulting in vascular leakage. Aitken and Sanford (1969a) found systemic anaphylaxis in cattle was manifested by pulmonary oedema, congestion and interstitial emphysema. Wells et al (1973) did not find interstitial emphysema but did note pulmonary oedema and congestion. This indicates that interstitial emphysema is probably not an integral part of anaphylaxis but a secondary lesion. Globule leucocytes do not appear to have been described in animals subjected to anaphylaxis. They were present in the bronchial tree of one calf but this animal had recently recovered from parasitic bronchitis (personal observations). Fog fever, by analogy with anaphylaxis, is likely to be initiated by oedema and congestion. An interesting observation in a very few cases of fog fever is that Schultz-Dale reactions in the pulmonary vein, using antigens derived from D. viviparus, result in very strong contractions of the vessel (Aitken and Sanford 1973). The positive Schultz-Dale reaction to lungworm antigens is not without relevance to the possible pathogenesis of fog fever, but in the absence of control animals any association is purely speculative. We have demonstrated the presence of reaginic antibodies to D. viviparus in cases of parasitic bronchitis and such

antibodies are also found in cases of fog fever (unpublished observations). It is highly likely that such antibodies are present in any animal which has experienced a lungworm infection, since parasites are very potent inducers of reaginic antibodies. Reaginic antibodies to D. viviparus are not confined to cases of fog fever.

Petechial haemorrhages were found on the epithelium of the trachea and bronchi of cattle subjected to anaphylactic shock and there were also epicardial and endocardial haemorrhages (Dungworth 1965; Aitken and Sanford 1969a). These lesions are seen, to a greater degree, in cases of fog fever and in some cases of post-patent husk. It is not known whether the haemorrhages are the result of capillary damage due to antibody : antigen reactions; or a secondary response in pulmonary congestion; or caused by vasoactive amines and similar substances. Vascular damage resulting from histamine, serotonin and bradykinin is likely in systemic anaphylaxis of cattle, in which intra-alveolar haemorrhage is a notable lesion. Vascular lesions consistent with an Arthus reaction have also been observed in bovine anaphylaxis (Dungworth 1965). Severe intra-pulmonary haemorrhage is not a common lesion in fog fever but does occur in anaphylaxis (personal observations).

Proliferation of alveolar epithelial cells is observed in many pulmonary diseases involving a large number of species; Omar (1964b) extensively reviewed the circumstances in which this lesion has been recorded. There are variations in the extent of alveolar epithelial hyperplasia in different diseases and the changes may be visible only microscopically, or extend to involve lobules, segments or whole lobes. It is not known if there is a basically similar proliferative stimulus which is applied in all circumstances. Although alveolar epithelial hyperplasia may be noted in many diseases of cattle, the most severe diffuse lesion has only been encountered in fog fever, post-patent parasitic bronchitis, diffuse fibrosing alveolitis and the pertussis reaction (q.v.).

Omar (1964a and b) reviewed the origin of alveolar epithelialisation and stated the two main interpretations :-

- the lesion was the result of alveolar epithelial hyperplasia
- or - the result of downward extension of proliferating bronchiolar epithelium.

Disagreement as to the origin of the cells was a reflection of lack of knowledge of the structure of the normal alveolus and the relationships of the various cell populations. Only recently have these questions been resolved and with them the origin of epithelial hyperplasia.

Use of the electron microscope has enabled the proliferating cells to be identified positively. The type 2 pneumonocytes lining the alveoli in fog fever are probably also the hyperplastic cells in complicated post-patent husk and the pertussis reaction, and form the cuboidal cell layer in fibrosing alveolitis (personal observations). Proliferation of type 2 pneumonocytes has also been identified in Jaagsiekte (Wandera and Krauss 1971; Perk et al 1971) which is thought to be a virus induced neoplasm; desquamative interstitial pneumonia and diffuse fibrosing alveolitis of man (Brewer et al 1969; Shortland et al 1969; Leroy 1969; Gould et al 1971; Farr et al 1970); lung responses to Freund's adjuvant (Faulkner and Esterly 1971), paraquat poisoning (Toner et al 1970; Butler 1970); Crotalaria poisoning (Kay, Smith and Heath 1969); cadmium fume pneumonitis (Carrington 1970); oxygen poisoning (Kistler et al 1967). Alley and Manktelow (1971) have also observed type 2 pneumonocyte hyperplasia in ovine pneumonia. If neoplasia is excluded, the cuboidal, hyperplastic, epithelial cells lining alveoli in the proliferative conditions investigated so far have consistently been found to be type 2 pneumonocytes. The actual cause of 'proliferative alveolitis' is not known, but it seems probable that this is a response to certain lung injuries comparable to neutrophil exudation of the suppurative pneumonias.

Focal proliferation of ciliated cells interposed with mucous cells has been seen in fibrosing alveolitis and farmer's lung of cattle. These cells may have arisen through metaplasia of the alveolar epithelium or by direct extension of bronchiolar epithelium through pores connecting some alveoli with bronchioles. This extension through Lambert's canals has been noted in fibrosing alveolitis of man (Spencer 1968). Nettesheim and Szakal (1972) investigated 'alveolar-bronchiolisation' in mice chronically exposed to synthetic smog or CaCrO_4 dust and found that bronchiolar epithelial cells extended through pores in the walls of bronchioles into adjacent alveoli. These results suggest that the ciliated and mucous secreting cells in alveoli are derived from bronchioles; this lesion is uncommon and does not represent the more usual morphology of alveolar epithelial hyperplasia.

Since type 2 pneumonocytes commonly proliferate to form a hypercellular lining layer, it is surprising that a hyperplastic lining layer composed of type 1 pneumonocytes has not been described.

The origin of type 1 and type 2 pneumonocytes in the adult animal has been presumed to be by division of mature cells of each type. Several investigations of cell dynamics in the respiratory tract have been undertaken, but the results are inconclusive since identification of the cell types and populations involved has been unsatisfactory or there has been insufficient consideration of the modern concepts of alveolar structure. Studies were made by Bertalanffy and Leblond (1953); Spencer and Shorter (1962); Bertalanffy (1964b); Shorter et al (1964) and (1966); Simnett and Heppleston (1966); Evans and Bils (1969). Cell populations in the lung have recently been more clearly identified. Pulmonary interstitial cells, which multiply to form a proportion of the alveolar macrophages, represent one

multiplying cell population (Bowden et al 1969) and type 2 pneumonocytes, which can differentiate, under some circumstances, to form further type 2 pneumonocytes and type 1 pneumonocytes are another (Evans et al 1973). It is possible that there are others. Evans et al (1973) have recently presented results indicating that some type 1 pneumonocytes develop from type 2 pneumonocytes in rats exposed to NO₂ gas. If these findings are also true for the normal lung, then type 2 cell hyperplasia would represent proliferation of the stem cell before maturation and explain why type 1 cell hyperplasia is not found.

Experience with field cases of fog fever suggests that extensive alveolar epithelial hyperplasia is not likely to be seen before the third day of illness. A more accurate determination was possible in the pertussis experiment (described later) where a degree of alveolar epithelial hyperplasia comparable to that found in the severest forms of fog fever was noted 96 hours after the start of the experiment. These two observations would suggest that three to four days is required for alveolar epithelial proliferation to extend through the lung.

Theoretical considerations of this point would depend on observations of alveolar size, cell size and turnover time which have not been made in the cow. Evans et al (1973) found that most cell divisions of type 2 pneumonocytes were over in 12 hours, that the period of DNA synthesis was 7.7 hours and that mitosis lasted 1.8 hours. The time for transition from type 2 to type 1 pneumonocyte was estimated at 24 to 72 hours. Weibel (1963) calculated the surface area of a human alveolus to be 270,000 sq. microns and Meyrick and Reid (1970) estimated that in each alveolus there were 113 type 1 cells (covering an area of 259,000 sq. microns) and 170 type 2 cells (covering an area of 11,000 sq. microns). If type 2 cells were to proliferate to

occupy the entire surface area of the alveolus, then approximately 4286 cells would be needed and these would be present during the 5th mitotic division of the original 170 cells. If the cell division time were 12 hours, then a minimum period would be 60 hours, assuming minimal time at rest. These figures are highly hypothetical and the errors may be great; it is assumed that none of the original 170 cells was destroyed. It illustrates, however, that on theoretical grounds one might not expect to see diffuse alveolar epithelial hyperplasia before the third day of illness, assuming that the stimulus to proliferation is applied at the start of the illness.

The fate of the alveolar epithelial cells in fog fever is not known but presumably they are sloughed into the alveolar spaces and pass into the bronchioles along with the macrophages.

The stimulus for this explosive proliferation of cells is not known. Omar (1964b) speculated on the likely causes but admitted that these were obscure, except in specific viral or toxic disorders where a direct effect upon the cells might be implied. Pulmonary oedema has often been implicated as a cause (Miller 1937) since this lesion often precedes epithelial proliferation but not all examples of pulmonary oedema are accompanied by epithelial hyperplasia (Hesse and Loosli 1949). In fog fever, evidence of early alveolar epithelial proliferation may be found in fatal cases affected by pulmonary oedema and congestion, which implies that the stimulus to cell multiplication could be applied at the same time^{as} or before, oedema was initiated. In that case, pulmonary oedema would not be the direct stimulus to proliferation. However, it seems very likely that pulmonary oedema and alveolar epithelial hyperplasia may be intimately connected. It has been postulated that in paraquat poisoning, a proliferative alveolitis, the poison damages the type 2 cells, which then fail to produce surfactant: the loss of surfactant is expected

to lead to transudation into the alveoli, causing pulmonary oedema. Proliferation of type 2 cells would then be a response to replenish the surfactant (Manktelow 1967; Cambar and Aviado 1970).

These same events may be explained in an alternative manner, which might also indicate why only certain types of pulmonary oedema result in hyaline membranes and alveolar epithelial proliferation. Pulmonary oedema fluid in some cases might be serum or plasma containing fibrinogen. Experimental results indicate that plasma or fibrinogen in the alveolar spaces can inhibit surfactant (Heshiki et al 1969; Said et al 1965; Taylor and Abrams 1966). Inactivation of surfactant might stimulate type 2 cells to proliferate and prolong the pulmonary oedema.

There is no proof that simple oedema can cause the alveolar epithelial cells to multiply. We have catheterised bovine lungs and infused pooled serum from adult cattle into the alveoli in large volume over several days without stimulating such cell division (unpublished observations). This process may not be mimicking a drastic pulmonary oedema, involving disruption of cell to cell contact, necrosis, anoxia and the release of pharmacologically active compounds into the circulation, such as might occur in fog fever. Fatal pulmonary oedema in anaphylaxis of cattle was not accompanied by alveolar epithelial hyperplasia (Aitken and Sanford 1969a) but it may be that the cattle in this trial died too acutely for the lesion to develop. Dungworth (1965), who subjected cattle to a less profound shock, did observe focal alveolar epithelial proliferation in animals surviving longer than those used by Aitken and Sanford (1969a).

In fog fever, diffuse alveolar epithelial hyperplasia might result from widespread inactivation of surfactant by plasma proteins including fibrinogen and be a reparative response aimed at restoring

surfactant levels. Loss of cell to cell contacts due to the local action of histamine or other mediators might also be involved. Alveolar epithelial hyperplasia is only occasionally a fatal lesion in fog fever, when it is particularly diffuse and complicated by oedema and interstitial emphysema.

Type V hypersensitivity has been discussed by Geil and Coombs (1968) and Roitt (1971): it might be summarised as a stimulatory hypersensitivity in which non-complement-fixing antibodies directed against cell surface components stimulate rather than destroy the cell. Such stimulation might occur as a result of the action of antibodies directed against mitotic inhibitors in the circulation.

Limited evidence indicates that immunological mechanisms might be implicated in the proliferation of alveolar epithelium, although the lung has been surprisingly neglected in the field of auto-immunity. Read (1958) produced pulmonary damage in rats by intra-tracheal injection of anti-rat-lung serum, believed to be specific for the alveolar epithelium. The changes which were described included alveolar epithelial hyperplasia. This work has not been systematically developed since, but advances in immunology and knowledge of pulmonary disease make it likely that this aspect will prove to be of importance in some circumstances, such as in diffuse fibrosing alveolitis.

At least three and probably four days of illness are required to develop diffuse alveolar epithelial hyperplasia yet only one of the eight fatal cases surviving for this period had extensive proliferation. It may be that only a proportion of animals develop widespread alveolar epithelial hyperplasia and these animals have some complicating disability, possibly pre-existing anti-lung antibodies from previous respiratory disease.

In cattle, hyaline membranes are most commonly found in parasitic bronchitis, fog fever and occasional cases of neonatal hyaline membrane disease. Jarrett (1957) performed histochemical studies on hyaline membranes in the lungs of cattle and his results were consistent with an origin of the membranes from transuded plasma. The membranes gave some, but not all, of the staining reactions of fibrin, which suggested that they were not formed solely from this material. Hyaline membranes have been extensively studied in man, since neonatal respiratory distress associated with the formation of extensive hyaline membranes is a common clinical problem. Interesting observations have been made in this condition, although extrapolation of these to the ox is only tentative. Montgomery (1956) claimed he had found fibrin by histochemical methods in the lungs of infants affected by hyaline membrane disease, but specific demonstration by immunofluorescence (Gitlin and Craig 1955) and electronmicroscopy (Van Breemen et al 1957) was required to confirm this. Fibrillar material, similar to fibrin, may be seen in the alveolar spaces of cases of fog fever with the electron microscope.

Lieberman and Kellogg (1960) discovered a deficiency^{ci} of the pulmonary tissue activator of plasminogen (profibrinolysin) in neonatal hyaline membrane disease. Fibrinolysis in man has been reviewed recently (Fearnley 1971) and comparative aspects in other animals have been examined (Hawkey 1971). Briefly, plasminogen activators in tissues initiate the formation of the protease plasmin from a blood precursor, plasminogen: plasmin effects the enzymic liquefaction of blood or fibrin clots. Antiplasmin, a plasmin inhibitor, neutralises any plasmin liberated in fluid blood. There is a wide range of concentration of plasminogen activator in different

tissues and among different species (Astrup 1966). A particularly wide species variation in tissue plasminogen activator concentration occurs in the lung (Albrechtsen 1957) and, significantly, the bovine lung contains large quantities of a trypsin inhibitor which also inhibits fibrinolysis (Astrup 1952). It has been postulated that the bovine lung is particularly liable to fibrosis after tissue injury because it is deficient in plasminogen activator and rich in fibrinolysin inhibitor; this results in delayed fibrin resorption (Astrup et al 1968).

It is likely that fibrinogen and pulmonary surfactant become bound up in hyaline membranes, since it has been demonstrated that surfactant inhibits clot lysis and fibrinogen inhibits the surface activity of surfactant (Taylor and Abrams 1964 and 1966). Surfactant may in fact have been demonstrated in hyaline membranes (Craig 1964).

Hyaline membrane disease has been extensively reviewed and the suggested aetiologies discussed (Nelson 1970). Emphasis in ideas of the pathogenesis has moved away from the postulated concentration of transuded plasma to the theory that membranes represent necrotic, sloughed epithelium from terminal and respiratory bronchioles. Barter et al (1966) have proposed that before the typical membranes appear: cells lining the airspaces degenerate, nuclear debris from these is mixed with the other constituents of the membrane and the whole takes on an eosinophilic appearance. A new epithelium then forms between the hyaline membrane and the underlying tissue, or cells grow over the membrane surface. After this, the membrane breaks up and passes into the bronchial tree or is ingested by macrophages, leaving the epithelium to revert to normal. Barter et al (1966) described the sequence of events in respiratory bronchioles in neonatal hyaline membrane disease. It is not possible

to correlate their results with the course of hyaline membranes in fog fever since the diseases are so different and the proliferative response in the alveoli is so noticeable in fog fever.

The basophilic streaks noticed in hyaline membranes in fog fever represent incorporated nuclear material, since they stain with haemalum and Feulgen. It is conceivable that this originates from trapped macrophages or from desquamated epithelial cells. No electron microscopical investigation of the early stage of fog fever has been carried out, because of the difficulty of obtaining live cases during the first 24 hours of illness. Where early proliferation of cells resulted in an obvious epithelial layer of flattish, cuboidal cells, this was often seen to be lifted from the alveolar walls. This may not represent in vivo sloughing since the material was always from animals which had died. If type 1 pneumonocytes did slough in the early stages of fog fever it would be impossible to tell with the light microscope, since these cells cannot be distinguished. It is possible, but not proven, that hyaline membranes in fog fever represent desquamated epithelial cells and macrophage debris intermixed with surfactant, fibrinogen and plasma proteins.

In cases of fog fever, eosinophils may be found in the lumen and lamina propria of the bronchial tree and in the alveolar spaces, alveolar septa and interlobular septa, especially in the early stages of the disease. Their number is less than that of parasitic bronchitis and much less than that of reinfection states (Weber and Rubin 1958; Michel and Mackenzie 1965; Mackenzie 1965). The role of the eosinophil is currently the subject of intense investigation and is generally taken to be connected with phagocytosis of immune complexes. Dungworth (1965) did not find pulmonary or circulatory eosinophilia during anaphylactic studies in the cow, but eosinophils

were found in NO₂ poisoned cattle (Cutlip 1965). Eosinophilia in the tissues may be related to the removal of antigen-antibody complexes in general; these are not necessarily the result of tissue damaging hypersensitivity reactions. The presence of eosinophils in fog fever does not imply, therefore, that hypersensitivity is involved in the aetiology. Parasitic infections are so common in cattle that interpretation of eosinophilia in the blood or tissues must be cautious. Many cases of fog fever were infected with Fasciola hepatica and Ostertagia ostertagi and these parasites may be routinely found at necropsy of normal adult beef cattle. In an area where lungworms are endemic, it is likely that adult beef cattle will be immune and that they will be repeatedly exposed to infection. Eosinophilia in the blood and even the lungs might be expected to be a constant finding in such animals. Pulmonary eosinophilia would probably necessitate the penetration of larvae or larval antigens to the lungs; this is possible since the fate of larval challenge in reinfection is not known. Eosinophilia in fog fever does not offer any clues to the aetiology of that disease. 'Pulmonary eosinophilia' in man is a term used to embrace a variety of disorders of uncertain aetiology characterised by lung shadows and blood eosinophilia (Crofton and Douglas 1969). Simple pulmonary eosinophilia has been attributed to pulmonary hypersensitivity to a number of antigens, including Ascaris lumbricoides and other parasites, drugs and pollens (Crofton and Douglas 1969). It is interesting that "fog fever" as a result of migration of Ascaris larvae in the lungs of cattle has been described on several occasions (Taylor 1952; Kennedy 1954; Allen 1962; Morrow 1968). These parasitic pneumonias do not have any bearing on classical fog fever but are exceptional causes of acute respiratory distress in singular circumstances where cattle have access to large numbers

of larvae. Fog fever is not comparable to pulmonary eosinophilia of man, therefore, in the same way that pre-patent or reinfection husk might be regarded.

Another cell population in the lung is represented by the interstitial cells and alveolar macrophages. Special stains for acid phosphatases demonstrate the increased numbers of interstitial cells in the alveolar walls in fog fever. These include blood monocytes in the capillaries, monocytes migrating into the tissues and interstitial cells already in the septal connective tissue. In the normal lung, large numbers of alveolar macrophages are lost into the bronchial tree each day and are carried out on the bronchial mucus. The greatly increased numbers seen in fog fever (and pneumonia) could be derived by division of interstitial cells; direct migration of monocytes from the blood; possibly mitosis of macrophages in the alveolar spaces; and even decreased rates of removal. Mitoses may be seen in alveolar septa with the light microscope in fog fever but the cell type cannot be identified positively. Bowden et al (1969) demonstrated division of interstitial cells to form macrophages and it is presumed that this process is occurring in alveolar septa in fog fever. Bowden et al (1969) also noted that some monocytes apparently formed free alveolar macrophages directly, without an interstitial phase. Multiplication of alveolar macrophages in the alveolar spaces has also been recorded.

Overall cell multiplication in the interstitial cell - alveolar macrophage population may well rival or exceed that of the type 2 pneumonocytes, but this may be masked by the constant loss of cells into the alveolar spaces and the consequent difficulty of demonstration. An indication of the total degree of cell multiplication may be taken from the weight of the lungs. In cases of fog fever

with extensive alveolar epithelial hyperplasia, the lungs may weigh some 8kgm. compared to a normal of 3-4kg. Such lungs are frequently not markedly oedematous and the increase in weight can be largely attributed to cells, indicating that an additional mass, equivalent to that of the normal lung, is mostly composed of macrophages, interstitial cells and type 2 cells.

Alveolar macrophages might migrate actively from the alveoli into the bronchioles and then be carried in the bronchial tree on the mucous blanket. Type 2 pneumonocytes might be lost in the same way, but, since they are not known to be actively motile, active passage cannot be assumed. It is believed by some that even the macrophages are passively carried on an upward moving film of surfactant, which is drawn into the bronchioles by the upward movement of the mucous blanket with which it is continuous. Type 2 cells might be removed in the same way.

The alveolar septa in some acini were dilated, stained blue with picro-Mallory and contained P.A.S. positive material. Most of the thickening was the result of septal oedema; in some septa there was a slight increase in collagen but not reticulin. This mild septal fibrosis was not accompanied by cellular infiltration by lymphocytes or plasma cells, although large mononuclear interstitial cells were apparent. There was only a focal increase in collagen and this was not found in more longstanding cases (e.g. 41, 42 and 43) or in the seven animals examined much later in the recovery stage. It is likely that resolution of intra-septal exudate would be accompanied by fibrosis but there is no indication that this would be progressive or associated with lymphocyte and plasma cell infiltration. Thus it is unlikely that a single incident of fog fever could develop into fibrosing alveolitis. Intra-alveolar exudates may also be organised

and incorporated into the septa by fibrosis (Spencer 1968).

Occasional obliterative lesions were found in bronchioles from the apical lobes in a minority of cases but these were very infrequent. Although plasma cells and lymphocytes were always present in the lamina propria of bronchi and in the peribronchial connective tissue these were not more numerous than in normal cattle. Saccular dilatations of the walls of bronchioles were attributed to previous pulmonary disease, since these may also be seen in cows with no history of fog fever. Bronchial epithelium in cases of fog fever was relatively normal, although globule leucocytes were found regularly. 'Tattering' and vacuolation, with large obliterative lesions comparable to those of post-patent husk, were not seen.

The pathological lesions in cases of fog fever are interstitial emphysema; pulmonary oedema and hyaline membranes; alveolar epithelial hyperplasia and globule leucocytes in the bronchial epithelium. These lesions are believed to be characteristic of the disease but not pathognomonic. Fog fever can be defined only by a combination of clinical, epidemiological and pathological terms.

The Parasitology of fog fever

Lungworms were not found on macroscopic inspection of the lungs of all 43 cases of fog fever. Baermann examination of material from 19 animals produced two and twenty larvae in two cases. A single worm was found in a histological section from one animal, which was negative on Baermann examination. Three of the nineteen cases had evidence of the presence of lungworms, but these were not discovered in numbers significant in terms of the known pathology of husk. In our experience, therefore, most cases of fog fever do not have demonstrable lungworm burdens. This does not necessarily mean that parasites are absent from the lung. Histological sections only represent a tiny proportion of the lung tissue and the fact that larvae or adults are not seen under the microscope means nothing. Larvae could be trapped in the lung, possibly by immune reactions or they could be dead for the same reason - in either case they would not appear after Baermann examination. Another explanation could be that only a small number of larvae reach the lungs of a sensitised animal and are immobilised and undetectable there. These larvae could stimulate the formation of 'blocking antibodies' after their penetration, which would prevent further challenge infections proceeding. Even if such a small larval dose was destroyed in the passage to the lungs, released antigens could be capable of inducing a hypersensitivity response in the lung or circulation, possibly in the pulmonary vein. This hypothesis could only be tested experimentally but it illustrates how the negative parasitological findings and lack of further signs after experimental challenge with D. viviparus do not necessarily exclude lungworm involvement in the pathogenesis of fog fever.

Again, if fog fever were a modified self-cure response any lungworm burden could have been shed by the time of necropsy.

Fog fever and other pulmonary diseases

Fog fever, post-patent parasitic bronchitis and atypical interstitial pneumonia of housed calves are three diseases with similar pulmonary pathology. The pathogenesis of these three diseases may have certain common stages, therefore, although it is not implied that the aetiologies are the same, since the diseases occur under different epidemiological circumstances.

We have not found any association between fog fever and farmer's lung in cattle.

Mackenzie (1966) mentioned cases of 'chronic fog fever' which had pulmonary lesions consistent with those of diffuse fibrosing alveolitis (D.F.A.) (Pirie and Selman 1972). There have been no examples of animals with fog fever progressively developing diffuse fibrosing alveolitis. The seven cases of fog fever examined in the recovery stage did not have fibrosis of the alveolar septa or cellular infiltration by plasma cells and lymphocytes. Fog fever has some parallels pathologically with desquamative interstitial pneumonia of man, although this latter disease has a more protracted course. Desquamative interstitial pneumonia (D.I.P.) is characterised by the proliferation, desquamation and accumulation of type 2 pneumonocytes in very large numbers in the alveolar spaces without marked alveolar septal fibrosis (Liebow et al 1965; Leroy 1969; Farr et al 1970; Gould et al 1971). Scadding and Hinson (1967) considered D.I.P. to be part of the general syndrome of diffuse fibrosing alveolitis, but this view is not shared by all workers (Rhodes 1973). It is possible that some cases of diffuse fibrosing alveolitis could be the result of repeated episodes of fog fever. The connection between diffuse fibrosing alveolitis and extrinsic

allergic alveolitis, particularly farmer's lung, can explain many cases of D.F.A. in the cow, particularly where precipitins are present in the sera and there is a history of respiratory disease in the winter. Not all cases can be attributed to farmer's lung and it is likely that some other factor is operative. In man hereditary factors and the use of certain drugs have been implicated (Crofton and Douglas 1969). In cattle, episodes of fog fever with diffuse oedema of alveolar septa and proliferation of type 2 pneumonocytes could be responsible. It is probably not necessary that the episodes of fog fever should be the dramatic form with severe dyspnoea that we have investigated. Other animals of the herd which show a more subtle degree of respiratory disability, perhaps not marked enough to be noticed by the farmer, may be affected by diffuse, mild pulmonary changes, precursors of interstitial fibrosis. It is also possible that recurrent pulmonary damage might be the result of repeated pasture changes, a toxic factor in lush grass, such as tryptophan or 3 methyl-indole, being responsible for the reaction. Such slight, regularly repeated, pulmonary insults could be expected to culminate in diffuse, massive pulmonary fibrosis of insidious onset after some time.

Mackenzie (1966) linked 'chronic fog fever' with exposure to dusts indoors and the cases he described can almost certainly be attributed to chronic farmer's lung (Wiseman et al 1973) or diffuse fibrosing alveolitis (Pirie and Selman 1972) not directly developing from an incident of classical fog fever. Mackenzie (1966) did not provide any evidence to suggest that his 'chronic fog fever' had any connection with the classical form. The present hypothesised association between fog fever, desquamative interstitial pneumonia and diffuse fibrosing alveolitis is an interesting speculation.

Fog fever and parasitic bronchitis

The possible relationship between fog fever and parasitic bronchitis has intrigued investigators since the early descriptions of these diseases. There is no doubt that many cases of so-called "fog fever" were actually examples of parasitic bronchitis and in our own survey there were 50 incidents of this in animals under two years of age. However, the pasture linked fog fever in adult beef-type cows, which has now been identified, can not be immediately connected with parasitic disease. Possible associations to be considered are that fog fever is:-

1. not related to parasitic bronchitis at all
2. a form of pre-patent husk
3. patent husk
4. post-patent husk
5. a form of reinfection husk
6. a hypersensitivity to lungworms
7. a hitherto unknown form of parasitic bronchitis.

If fog fever has no connection with parasitic bronchitis that fact will only be accepted when the cause of the syndrome is known, since lungworms are so common in Britain and there are so many similarities between the pathology of fog fever and some aspects of that of husk. One plausible hypothesis is that the lung lesions of fog fever are induced after the ingestion of tryptophan or some other chemical in the grass and there is some evidence to support this view. However, it has not yet been unequivocally demonstrated that the severest lesions of fog fever can be produced experimentally in adult cattle by the ingestion or administration of likely compounds at levels which may be related to those in grazing pastures in the autumn. If fog fever were a simple plant poisoning, it might be expected to

recur annually in the same animal, an observation not often made.

Also, if levels of such a toxic compound were related to lush grazing,

cases of fog fever might be seen more frequently in the spring months. We did not receive any cases at that time of year. It is possible that such incidents do occur, but they have not been demonstrated unequivocally in the literature. Tryptophan intoxication provides an illustration of how lesions comparable to those of fog fever can occur in the absence of lungworms and atypical interstitial pneumonia and the pertussis reaction provide others. At the moment, tryptophan and 3 methyl-indole ingestion has provided the most satisfactory explanation of how fog fever might develop without lungworms, but the relationship of this to the field situation has not been finally demonstrated. Globule leucocytes have not been recorded in tryptophan or 3 methyl-indole experiments and eosinophils were not particularly numerous in the lungs of the animals given these substances in our studies. If fog fever were the result of tryptophan ingestion, the globule leucocytes in the bronchi and eosinophilia in the lung might be a consequence of coincidental parasitic challenge during the grazing season. Such challenge would then have no bearing on the pathogenesis of the disease.

Hyaline membranes with pulmonary oedema, interstitial emphysema and alveolar epithelial hyperplasia are prominent in the lungs of calves in the pre-patent phase of parasitic bronchitis, days 7 to 25 after infection (Jarrett et al 1957). These changes are also found in fog fever. However, the most severe lesion in this stage of husk was hyaline membrane formation and there was also very severe damage to, and eosinophil infiltration of, the bronchial and tracheal epithelium (Jarrett, McIntyre and Urquhart 1957). The most severe lesion is alveolar epithelial hyperplasia in many instances of fog fever

and pulmonary oedema in others. Severe bronchial or tracheal lesions are not found in fog fever apart from marked haemorrhage in acute cases, a lesion not described in pre-patent parasitic bronchitis. The most severe lesions in pre-patent husk were found in experimental calves given 50,000 larvae; all these calves had died by 18 days after infection, when immature parasites were seen in the bronchial tree histologically (Jarrett, McIntyre and Urquhart 1957). If the fatal cases of fog fever were suffering from pre-patent husk then the infecting dose must have been much larger than 50,000 larvae on a body weight basis; some of these larvae would be recovered on Baermann examination and parasites would be seen readily in the airways: this is not the case. In addition, if the adult animals were exposed to such a heavy infection on the pasture then their calves at foot would probably develop severe signs of husk: this does not happen. Most deaths in the pre-patent phase of parasitic bronchitis occur in the third week after infection and clinical signs are not usually observed in the first week (Jarrett et al 1960).

Rubin and Lucker (1956) recorded fatal pre-patent husk $7\frac{1}{2}$ days after infection of a 2 month old calf, weight 120lbs, with 750,000 larvae; in this case clinical signs were not apparent until day 6 and 18,200 larvae were recovered from the lungs after death. Seven of the 24 fatal cases of fog fever died within 6 days of pasture change, and 21 of the 24 died within 12 days. This is not consistent with pre-patent husk except in the case of an astronomically large infective dose: on the same basis as Rubin and Lucker (1956) this would be 6,250,000 larvae for a 1000lb cow which had no immunity.

Pre-patent parasitic bronchitis is not likely to be the cause of fog fever.

Many cases of "fog fever" in young calves proved to be patent infections of D. viviparus: these animals should have been diagnosed as examples of husk in the first place. Fog fever is not patent husk because adult worms are not found in the vast majority of cases and only in single numbers then. Also, the pulmonary lesions are different from those of patent husk.

The question of an association between fog fever and post-patent husk is more difficult to answer. My clinical colleagues, who investigated the epidemiology of fog fever and performed the clinical examinations on the field cases, were satisfied that, from a clinical view, the two syndromes could be differentiated. However, we did not set out to investigate post-patent husk and there may well be aspects of that, yet to be discovered, which have a bearing on fog fever. We did not find cases of fog fever in young animals, all the incidents were of post-patent husk. The possibility remains that outbreaks of fog fever will be demonstrated in animals under two years of age: the crux of such a demonstration will be the exclusion of parasitic disease; this has not yet been done.

In the majority of cases of post-patent husk there is no difficulty in the diagnosis, pathologically, because extensive lesions of the patent phase are still present, along with interstitial emphysema, pulmonary oedema and hyaline membranes and alveolar epithelial hyperplasia. Worms may also be found without difficulty. In a proportion, however, the main lesion is severe, diffuse alveolar epithelial hyperplasia, every bit as extensive and dramatic as that of fog fever, in the apparent absence of parasites. In these instances the lungs of post-patent husk cases and those of fog fever cannot be separated on macroscopic inspection. Microscopical differentiation depends on multiple examinations of the bronchial tree. In the case of post-patent husk, there is bronchitis, bronchiolitis, tattering and desquamation

of the bronchial epithelium and very few globule leucocytes are to be found; multiple lung blocks may also reveal the presence of obliterative lesions in the bronchioles. Histological examination of fresh material in fog fever indicates that the bronchial epithelium is more normal, tattering and desquamation are absent (except in fatal cases where desquamation is an artefact), many globule leucocytes are present and there is minimal bronchitis and bronchiolitis. Except for the apical lobes, bronchiolar obliterative lesions are usually absent and parasites are very rarely found. Despite these differences, it is often very difficult or impossible to distinguish the two diseases pathologically on the basis of a small number of sections. The presence of a few parasites in the bronchial tree of a young animal is probably of significance in diagnosis, but it may be argued that the same number in an adult animal is less important. Certainly, in an animal in the first or second grazing season, the findings of lungworms at all in association with severe alveolar epithelial hyperplasia, oedema and hyaline membranes and interstitial emphysema must be strongly indicative of post-patent husk. A few worms in much older animals are less incriminating, since carrier animals are known (Jarrett et al 1954). The situation with regard to the post-patent stage can be summarised as : the diseases may be differentiated clinically and epidemiologically but pathologically, the differentiation is sometimes not possible. We have, however, reserved the term 'fog fever' for a pulmonary disorder of adult cattle. There are cases of respiratory disease in animals under two years of age in which the pathology is very comparable to that of fog fever and not immediately attributable to post-patent husk. Some of these animals may have a grazing history consistent with fog fever, in others the history may be unknown. Sometimes the material available for examination is

unsuitable or insufficient. If it is not possible to make a diagnosis of post-patent husk after considering the history, pathology and clinical signs, and the pulmonary lesions are diffuse pulmonary oedema with hyaline membranes, interstitial emphysema and alveolar epithelial hyperplasia, then the diagnosis should be "the respiratory distress syndrome". The lesions of fog fever are not pathognomonic and comparable pathology may be observed in A.I.P., the pertussis reaction, post-patent husk and tryptophan toxicity. Fog fever in adult beef-suckler cows is a clinico-pathological entity, and the integrity of this should be maintained in the interest of clarity.

Post-patent husk is discussed in another part of this thesis, but certain general aspects are relevant to this theme. Severe alveolar epithelial hyperplasia in this stage of the disease was said to occur in approximately one quarter of those animals which were severely affected in the pre-patent and patent phase (Jarrett et al 1960). That is to say, a severe deterioration took place in an animal which had already been exhibiting marked respiratory signs for some time. None of the cases of fog fever were noticed to have been ill in the preceding weeks. This does not rule out the possibility that disease was not noticed, but severe signs before the pasture change have not been recorded in the literature and the circumstantial evidence suggests that the animals are clinically normal at the time of movement. If fog fever were post-patent husk, one might expect a proportion of the cases to have obvious, small parasitic burdens and additional residual lesions of the patent stage, but post-patent husk of this type has not been identified in adult cattle.

There is clinical, epidemiological, pathological, parasitological and circumstantial evidence to suggest that fog fever is not the same syndrome as complicated post-patent husk. A basically similar reaction to the 'self-cure' response, which is believed to be the mechanism of

the post-patent phase, may be the cause of fog fever and this postulate is discussed below.

It seems likely that most mature animals in an area where parasitic bronchitis is endemic will have a high degree of immunity to lungworms. The reinfection phenomenon, which is observed in adult dairy cows, may be attributed to a heavy larval challenge of animals with waning or low immunity after a period of low exposure, although the pathogenesis of this syndrome and the fate of the larval challenge have not yet been fully worked out (Jarrett et al 1960; Michel and Mackenzie 1965; Selman et al 1973b unpublished). We have not encountered this type of clinical reinfection respiratory disease in beef cattle; if this distinction is real, a difference in husk epidemiology between dairy and beef herds is implied. Pulmonary lymphoid nodules are an integral part of the pathology of the reinfection phenomenon; these were not present in the lungs of fatal and non-fatal cases of fog fever. Pulmonary lymphoid nodules were noted in the lungs of the seven animals slaughtered more than one month after developing fog fever. This illustrates that beef cattle can produce pulmonary lymphoid nodules but does not show that these are clinically significant, since animals going onto a new field in an endemic area might well be expected to pick up a fresh larval challenge incidental to some other factor - such as a grass toxin. When we infected seven recovered cases of fog fever with 30,000 larvae of D. viviparus, there were no subsequent respiratory signs. Two other mature beef cows were each given 100,000 larvae and also failed to develop any respiratory disease in the succeeding two months (unpublished observations). All these animals were obviously immune to D. viviparus at the time of challenge. In the case of the seven fog fever animals described in the provocation tests, it could be

argued that they were not immune at the time of the last pasture change, that fog fever was a reinfection response and that immunity to further infection developed before our challenge. Against this is the dissimilarity between the pathology of reinfection states (Jarrett et al 1960; Jarrett and Sharp 1963; Michel and Mackenzie 1965; Pirie et al 1971c) and the lung lesions of fog fever and differences between the clinical signs and epidemiology of reinfection and fog fever. The possibility of an unappreciated form of reinfection response peculiar to beef cattle has not yet been explored. This could possibly be done by taking a number of adult beef animals about to move pasture and challenging them with a large dose of larvae: this experiment has not been attempted, although our experience with 2 animals would suggest that it would not result in severe clinical signs. Furthermore, if a heavy challenge were to be found on the new pasture, the calves at foot might be expected to develop severe parasitic bronchitis. Fog fever cannot be held to be the reinfection phenomenon noted in dairy cattle.

It has often been claimed that fog fever is a 'hypersensitivity' or allergy to lungworms and it has been proposed that challenge of recovered cases of fog fever with lungworm larvae can reproduce the fog fever syndrome (Weisman 1970). When we challenged seven recovered cases of fog fever with lungworms there was no untoward effect. If fog fever were a simple hypersensitivity to D. viviparus, then further respiratory signs should follow repeated exposure to the antigen. Our experimental results indicate this is not the case and the absence of proven examples of repeated attacks of fog fever in the same individual would support this. It may be that blocking antibodies, inhibiting lungworm infections, develop in cases of fog fever during the recovery phase and this possibility has not been

investigated. Such blocking antibodies might prevent penetration of lungworm larvae from the gut into the lymphatics. If blocking antibodies are to be found, it is conceivable that the intestinal wall would be the site of action, but the point at which infections are terminated in immune animals has not yet been determined. One way round such a block would be to administer larvae by routes other than per os. Weisman (1970) gave an intravenous injection of lungworm antigens to a cow which was thought to have recovered from fog fever and the cow rapidly developed respiratory distress and died. This response is very suggestive of anaphylaxis (Aitken and Sanford 1969a; Eyre et al 1973), a syndrome which appears to be different from fog fever in many ways. It is possible that any adult animal which is immune to lungworms would undergo anaphylactic shock after intravenous challenge with D. viviparus antigens. In an area where lungworms were endemic, all adult animals might be immune. The results of Weisman (1970) in this single case do not have any relevance to the pathogenesis of fog fever. The evidence supports the view that fog fever is not a simple allergy to lungworms. Suggestions of a complicated aetiology involving blocking antibodies and type 1 hypersensitivity lack experimental proof.

Fog fever may be the result of a reaction which does not involve lungworms at all since the established patterns of parasitic bronchitis are not consistent with all the facets of our understanding of fog fever, but there may yet be lungworm mediated reactions of which nothing is known. One aspect of husk which has been unexplored is the pathogenesis of the post-patent lesions. The similarity between certain cases of complicated post-patent husk, in which diffuse alveolar epithelial hyperplasia is found, and fog fever has already been mentioned. The examples of complicated post-patent husk which

we examined were all from field outbreaks of the disease. The degree of alveolar epithelial hyperplasia in experimental cases of husk (Jarrett et al 1955, Jarrett, McIntyre and Urquhart 1957) is difficult to estimate but seems to have been less extensive than that recorded in field cases of the disease (Jarrett et al 1954). It has been noted that alveolar epithelial hyperplasia tends to be common to all the animals examined at postmortem in certain outbreaks of husk (Jarrett et al 1954) and it is remarkable that only a proportion of cases should develop this most severe lesion. It is conceivable that some other factor is operating in instances of complicated post-patent husk, which emphasises the alveolar epithelial hyperplasia and makes the lesion more diffuse. If this factor is confined to field cases it could well be associated with pasture change, which is frequently recorded in our case histories. Self-cure can obviously proceed in husk without pasture change, since the disease progresses in housed animals. Self-cure in other parasitic infections may be induced by pasture change alone however (Allonby 1972). The hypothesis in regard to field cases of post-patent husk is that pasture change at about the time of normal self-cure may heighten the response in such a way as to produce some of the extreme examples of alveolar epithelial hyperplasia mentioned above. That is to say the lesions due to post-patent husk could be compounded by lesions resulting from tryptophan or indole ingestion; it might not be possible to distinguish these. The possible aetiologies of post-patent husk need to be investigated further. These unknown factors in the pathogenesis of the post-patent reaction raise the possibility that fog fever may be an unusual manifestation of this self-cure or post-patent reaction. There is no proof that fog fever is a post-patent stage (i.e. 55-70 days) after an initial lungworm infection. There is a possibility that fog fever is the result of the self-cure

reaction having been set in motion by some other factor. In this respect, it is interesting to note that tryptophan and 3 methyl-indole may possibly have a role in the induction of self-cure associated with pasture or dietary change in other animals (Allonby 1972).

The close similarity between post-patent husk and fog fever coupled with the experimental implication of chemical mediators in this type of reaction provides a strong possibility that there is a link along a final common pathogenic mechanism. Many unexplored aspects of lungworm infection, particularly the pathogenesis of post-patent husk and reinfection responses, might yield information of value in understanding these reactions.

Roberts (1973) stated that diethylcarbamazine was of value in the treatment of some cases of 'fog fever' and attributed this to the ability of this drug to inhibit systemic anaphylaxis. Diethylcarbamazine is an inhibitor of slow reacting substance A (S.R.S.A.) (Orange et al 1968) and strongly reduces the anaphylactic response in calves, provided it is given before the challenge (Eyre et al 1973). In our field survey, cases of pre-patent and patent parasitic bronchitis were encountered, these were claimed to be examples of 'fog fever'. Diethylcarbamazine has been used as an anthelmintic for many years; it seems likely that this property of the drug is separate from its ability to inhibit S.R.S.A..

The Aetiology of Fog Fever

It has been hypothesised that fog fever is the result of an anaphylactic response in the lung; parasitic bronchitis; tryptophan, 3 methyl-indole or other chemical intoxication from grass. In certain circumstances, all these three suggested causes may act on the lung to produce lesions comparable to those of fog fever and it seems likely that they may act in a common manner. However, fog fever has not been clearly demonstrated to be the result of any of these agents and the aetiology is still unknown.

Anaphylaxis might explain the rapid onset of signs in fog fever, but severe, diffuse, alveolar epithelial hyperplasia has not been produced as a result of anaphylaxis (Aitken and Sanford 1968; 1969a, Wells et al 1973). Dungworth (1965) did produce some focal alveolar epithelial hyperplasia, but this was after aerosol challenge and the pulmonary pathology was in other respects consistent with an Arthus reaction. Anaphylaxis has proved rapidly fatal in most trials and severe intrapulmonary haemorrhage has been observed at postmortem. This may be a dose response. All the lung lesions of fog fever have not been demonstrated after anaphylactic shock and the relevance of this procedure to sensitisation and antigen challenge in the field is unclear. It may be postulated that the antigen is D. viviparus, which produces sensitisation by repeated low level infestations and anaphylaxis after re-exposure. There is no proof that this is so.

Fog fever is not one of the accepted forms of parasitic bronchitis but an unknown role for this parasite can not be excluded from the pathogenesis. The possible relationships between fog fever and husk are examined above.

Fog fever could well be the result of the ingestion of tryptophan, 3 methyl-indole or related compounds from grass, but again there is no direct evidence relating experimental findings with the field situation. Pulmonary lesions comparable to those of fog fever can be induced by ingestion of these compounds, but severe diffuse alveolar epithelial hyperplasia has not been clearly demonstrated. These chemicals occur in grass, but whether they are in the concentration necessary to produce disease at certain seasons is not known. This line of research appears promising and this hypothesis seems to be the most likely explanation of the aetiology.

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DIFFUSE FIBROSING ALVEOLITIS AND EXTRINSIC ALLERGIC ALVEOLITIS
IN CATTLE

INTRODUCTION

During our investigations into fog fever, we recognised the existence of two respiratory conditions not previously defined in cattle in Britain; these were very similar to diffuse fibrosing alveolitis and extrinsic allergic alveolitis (farmer's lung) of man. The clinical and pathological features of these bovine diseases have been discussed (Pirie and Selman 1972; Pirie et al 1971a; Wiseman et al 1973) and the syndromes will be further defined, when the details of a large series of cases are available (to be published). A number of the animals submitted as cases of fog fever during the field survey were found to be affected by diffuse fibrosing alveolitis or extrinsic allergic alveolitis and the pulmonary lesions in these cattle are described below.

DIFFUSE FIBROSING ALVEOLITIS

Clinical History

All the cattle were adult cows of beef and dairy breeds and were affected by a chronic respiratory disorder, characterised by hyperpnoea, tachypnoea, non-productive coughing, exercise intolerance and widespread crepitations over both lung fields. Occasionally there was also congestive heart failure, the result of cor pulmonale, and evidence of hepatic or renal disease. There was usually a history of progressive, gradual onset of respiratory signs over weeks or months, or of repeated, acute, severe, respiratory signs from time to time; there was no accurate anamnesis in a minority of animals. The percentage of circulating eosinophils was usually elevated although the total white cell count remained within normal limits. In only one animal were severe clinical signs first noticed after a change of pasture (case E).

Significant points in the history of each animal are summarised in table (13).

Postmortem Findings

The pulmonary pathology of even the most severely disabled animals was usually unimpressive on superficial visual inspection. Close examination and palpation revealed the presence of severe, diffuse pulmonary lesions, which differed markedly from those found in either bronchopneumonia or proliferative pneumonia of cattle.

The lungs were markedly heavier than those of normal cattle and usually weighed between 6 and 12 kilograms; the normal lung weight is 3-4 kilograms (Sisson and Grossman 1962) although occasional normal lungs up to 5 kilograms have been recorded (personal observations).

All the lungs were weighed without mediastinal or bronchial nodes and after section of the trachea just anterior to the origin of the lobar bronchus of the right apical lobe. There was marked pallor of the lungs of slaughtered, exsanguinated cattle and clear colour changes of many lung lobules were apparent in fresh material (Figs. 46,47). Many lobules were very pale pink, even white in colour, markedly over-inflated, especially at the periphery, and contained a number of grey foci, which were sometimes shown to be unusually prominent, thickened bronchioles. Other lobules were slightly collapsed below the rest of the lung surface, greyish red in colour and very oedematous (Figs. 48,53); abundant clear fluid ran from the cut surface of such tissue and the thickened bronchioles were greenish-yellow in colour. Chalky, yellow coloured lobules, which contained a number of slightly depressed small grey spots, were also noted and these lobules were found to be very firm and heavily fibrosed on cross section. Localised, smooth, white, solid, very cellular areas were identified in some yellowish or pale pink lobules after sectioning (Fig. 50) and these zones were more clearly demarcated in tissue sections fixed overnight in formalin (Fig. 51). Cystic change was observed in some lung lobules and in such sites there were air spaces of uneven size and gross distortion and destruction of acinar architecture by diffuse intra-lobular fibrosis. Pale, white, fleshy, firm lobules predominated in the lungs of animal E (Fig. 49); these were the result of particularly severe fibrosis and alveolar epithelial hyperplasia.

Abnormal lobules were apparent in all lobes of the lungs, but overinflated lobules were more numerous in the apical lobes; there were frequent areas of severe fibrosis in the dorsal cardiac lobes and in the pulmonary tissue about the hilus of the lungs, where

yellow lobules were regularly found. The overall impression was of very pale, very heavy, diffusely fibrosed pulmonary tissue. Fibrous pleural tags (Fig. 46) were often noted over the ventral surfaces of the diaphragmatic lobes and at the edges of all lobes, though obvious pleurisy was not regularly observed. There was (Fig. 66) fibrosis and thickening of the interlobular septa, which were often seen to be grey in colour. The lobules failed to move apart when the lung lobes were sectioned, so that in consequence the cut surface of the lobes was usually very even in outline. Little or no interstitial emphysema was observed and pulmonary oedema was mild or insignificant, although in some cases these two lesions were more developed. The bronchial tree and trachea were occasionally clean, but in most animals there was an excess of thick mucus (Figs. 52, 53), which was in the form of scanty, greyish-green globules; more abundant, thick, yellow-green or grey strands; or a heavy, muco-purulent exudate of considerable quantity. Mucous plugs were found in the segmental bronchi and were occasionally associated with wedge shaped areas of acinar collapse, especially at the periphery of the lobes. Frank pus was not often apparent in the bronchial tree and, when present, usually localised to one lobe or an area of bronchiectasis.

Macroscopically the pathology was not dramatic but there were marked pulmonary lesions in all sections of tissue from all lobes of the lung on microscopical examination; these usually involved the whole lobule, but in some instances there were apparently normal groups of acini in a partially affected lobule.

Mucus, infiltrated by neutrophils, macrophages and in some cases eosinophils, was found in varying quantities in the trachea, bronchi and bronchioles in histological sections, and there was an occasional purulent exudate in some lobes. The extent of the mucus in

the histological sections corresponded to the gross distribution of mucus in the bronchial tree. In a minority of animals, organising intra-bronchiolar exudates or foci of bronchiolitis obliterans were noted in a number of the lung sections and then the associated acini were usually grossly overinflated. Globule leucocytes were numerous in the bronchial epithelium at all levels and there were many other intra-epithelial cells, principally neutrophils, with smaller numbers of eosinophils and plasma cells. The cell population of the lamina propria was varied; there were always plasma and lymphoid cells and these were sometimes arranged in aggregates and heavy concentrations; neutrophils were regularly present, sometimes in large numbers, whereas eosinophils were less often noted and were usually found in small or moderate numbers. Oedema and congestion of the lamina propria were not observed. The bronchial mucous glands appeared to be increased in number, volume and complexity in some animals and, although point counting measurements were not made, a definite impression of hyperplasia remained. The hyperplastic glands were dilated, particularly coiled, and extensive, both within and without the bronchial cartilage. Globule leucocytes were occasionally observed in the epithelium of the mucous glands in the lamina propria. On gross inspection, there was always a large quantity of mucus in the bronchial tree of the animals which were subsequently thought to have hyperplasia of the mucous glands. A constant peribronchial infiltration by plasma cells and lymphocytes was frequently found and this varied in degree, as did the extent of peribronchial fibrosis.

Occasionally, there was hyperplasia of the bronchiolar epithelium and mitotic figures could frequently be observed in such sites. In a minority of cases, there was a 'squamous metaplasia' affecting some bronchioles in some sections of the lung. Bronchioles

were empty, or contained a mixed cellular exudate (Fig. 54) of neutrophils, macrophages and a small proportion of eosinophils. Hyaline material, which was intensely streaked with basophilic strands, was frequently found in the bronchioles and alveolar ducts (Fig. 56), where it was infiltrated by macrophages and neutrophils; eosinophilic hyaline deposits were also noted in these same positions. When a large quantity of mucus was present in the bronchial tree, there were frequently mucous plugs in the bronchioles, and the mucus often extended, in such cases, into the alveolar ducts and the alveoli (Fig. 63), which were occasionally lined by apparently metaplastic epithelium. Plasma cells and lymphocytes were found in the lamina propria of the bronchioles, along with neutrophils and some eosinophils. There was a constant peribronchiolar infiltration of lymphocytes and plasma cells also (Fig. 54). Bronchiolitis obliterans or organising intra-bronchiolar exudates affected some lobules in the lungs of a number of cattle.

The most striking lesions were found in the respiratory acini.

Many alveoli were empty and some contained only oedema fluid and globular, eosinophilic, hyaline deposits infiltrated by macrophages, neutrophils and occasionally multinucleated giant cells, but in most there was a marked, large mononuclear cellular exudate (Figs. 55, 56). This was composed partly of cells which had the appearance of alveolar macrophages, with an indented bean shaped nucleus, abundant eosinophilic or finely vacuolated cytoplasm, and which occasionally contained phagocytosed red blood corpuscles or hyaline material. Similar sized cells with slightly basophilic cytoplasm, which was finely vacuolated, and round hyperchromatic nuclei predominated in alveoli lined by hyperplastic epithelial cells (Fig. 57). The epithelial and free cells could not be differentiated with the light microscope, although the

nuclear shape and absence of cytoplasmic phagosomes suggested that some of the free cells were type 2 pneumonocytes. The free cells were so numerous in many instances that the lumen was completely filled by as many as 60-70 cells, in which mitotic figures were commonly found. Neutrophils and occasionally eosinophils were present but were never the predominant cell type, except in localised areas of bronchopneumonia. Multinucleated giant cells and occasional intra-alveolar haemorrhages were observed. Eosinophilic hyaline membranes were never well developed, although in some alveoli hyaline material was seen as clumped, whorled deposits infiltrated by phagocytic cells, or as basophilic streaked deposits similar to those found in the alveolar ducts and bronchioles (Fig. 56).

There was frequently diffuse hyperplasia of the alveolar epithelium and the alveoli were then lined by cuboidal or low columnar cells (Figs. 57,58). These had a basally situated, hyperchromatic, round nucleus and a variable amount of slightly basophilic cytoplasm, which frequently contained a small number of large clear vacuoles. Mitotic figures were frequently found in these cells. The hyperplastic cells were sometimes arranged singly, discretely, and slightly apart on the alveolar septum (Fig. 57); or as a continuous, tightly packed, cuboidal epithelial lining layer (Fig. 58); or as a double or triple layer of cells, which projected into the lumen (Fig. 60). Desquamated cells, closely resembling those of the epithelium, were found free in the lumen and were difficult to distinguish from the alveolar macrophages (Figs. 54, 57). Cuboidal epithelial hyperplasia always predominated in the majority of affected acini in the lungs but in most animals it was possible to find multiple foci in which the acini were lined by tall, columnar, ciliated cells (Fig. 61), or by a mixture of ciliated and mucus secreting columnar cells (Figs. 62, 63); in

this latter instance the alveoli were frequently filled by mucus (Fig. 63). The tall columnar lining epithelium was not confined to alveoli adjacent to bronchioles, but was found in alveoli (Fig. 57) at the periphery of the lobule, as a localised lesion affecting a group of acini. The change to columnar epithelium was never a diffuse lesion affecting the majority of acini in the lobule. Where alveoli adjacent to the bronchioles were affected, it was sometimes possible to trace the abnormal alveolar epithelium through fine openings in the wall of the terminal bronchioles and to demonstrate continuity with the epithelium of the bronchiole. When acini away from the bronchioles were affected, it was not clear whether the abnormal epithelium was the result of metaplastic change of the alveolar epithelial cells or caused by growth of bronchiolar epithelial cells into the alveoli. The mucus secreting cells appeared to be active in some acini, where the alveoli were filled with mucus, but some of the mucus may have passed by reflux action from the bronchioles into the alveoli.

The alveolar septa were severely affected by two main lesions; these were interstitial fibrosis and dense cellular infiltration by plasma cells and lymphocytes. Although these lesions were always found together, the degree of each varied from case to case, and it was possible to classify each set of lungs as being predominantly affected, as a whole, either by alveolar septal cellular infiltration or alveolar septal fibrosis (Table 15).

The cellular lesion (Figs. 56, 58) was characterised by a massive influx of mature plasma cells, with lesser numbers of lymphocytes and a proportion of macrophages, neutrophils and eosinophils, into the alveolar septum, which was often thickened to a size greater than that of the alveolus. Large aggregates of plasma cells and lymphocytes were regularly found in the alveolar septum and there was distortion

and obliteration of many alveoli as a result of this septal thickening (Fig. 56). When the cellular infiltration was heavy, there was always increased collagen and reticulin deposition in the septum also.

The fibrosing lesion was seen as a massive increase in the amount of collagen and reticulin in the alveolar walls and as distortion, destruction and obliteration of alveolar lumina (Figs. 59, 63, 64, 65). Fibroblasts were frequently found in the thickened alveolar septa along with elongated, mononuclear cells which resembled interstitial cells. Plasma cells and lymphocytes were constantly noted in the fibrosed septa although the numbers varied greatly, from very few to a large number. Mast cells were abundant in the alveolar septa of both the cellular and fibrosing forms, but were particularly numerous in the heavily fibrosed septa (Fig. 64). Incorporation of resolving intra-alveolar exudates into the alveolar wall by fibrosis was observed in some acini and this resulted in obliteration of the lumen. Hypertrophy of the smooth muscle of the alveolar ducts was noted in some animals.

There was often heavy collagen deposition in the interlobular septa and aggregates of lymphocytes and plasma cells were frequently observed in the connective tissue. Giant cells and macrophages were found in the lymphatic vessels in moderate numbers. Oedema, interstitial emphysema and aggregates of eosinophils were not usually present.

The pulmonary lesions in each case were of the pattern outlined above, although the various lesions differed in degree in each case. Postmortem findings in individual cases are set out in appendix 2, but significant points in the pathology of each animal are given in table (15). Large mononuclear cell accumulation in the alveolar spaces was most marked in animals F and E; alveolar septal fibrosis was most extensive in H and cellular infiltration most noticeable in C. All the lesions described could be found in some sections of all cases.

Lesions in other organs than the respiratory tract were frequent in these cattle. Cor pulmonale was observed in three cases; in these animals there was an enlarged right ventricle, with an increase in the thickness and mass of muscle, and dilatation of the pulmonary arterial trunk to a diameter exceeding that of the aorta (Figs. 68, 69, 70). Hepatic fibrosis was another common observation; this was the result of cirrhosis or infestation with Fasciola hepatica. One animal (E) was found to have numerous gas bullae in the mediastinal lymph nodes and many of these bullae were filled with blood (Fig. 67).

ANIMAL	AGE	BREED	SEX	DATE OF EXAMINATION	PRECIPITINS TO MICROPOLYSPORA FAENI
A	Adult	Friesian	F	November	+ve
B	4y	Friesian	F	November	+ve
C	Aged	Friesian	F	March	+ve
D	8y	Galloway	F	January	+ve
E	6y	Ayrshire	F	September	+ve
F	7y	Hereford x	F	June	-ve
G	Aged	Highland	F	March	-ve
H	8y	Shorthorn	F	January	-ve
J	3y	Galloway x	F	July	-ve
K	6y	Friesian	F	March	not done

Table (13). Diffuse fibrosing alveolitis: significant points from the history of each of ten cases of this disease.

ANIMAL	AGE	BREED	SEX	DATE OF EXAMINATION	PRECIPITINS TO M. faeni
A	4y	Galloway	F	February	+ve
B	Adult	Galloway	F	August *	+ve

* This animal was affected by respiratory disease in March.

Table (14). Significant points from the history of two cases of bovine extrinsic allergic alveolitis (farmer's lung).

Animal	Main Lesion in Alveolar Septa	Mononuclear Cells in Alveolar Lumen	Other Lesions
A	Cell infiltration	Few	Hepatic fibrosis; abomasal ulceration.
B	Fibrosis	Few	Cor pulmonale; renal amyloidosis.
C	Cell infiltration	Many focally	Cor pulmonale; hepatic fibrosis, amyloidosis.
D	Fibrosis/cell influx	Many focally	Fasciola in liver.
E	Fibrosis	Very many	Bile duct fibrosis and calcification.
F	Cell infiltration	Very many	Fasciola in liver.
G	Fibrosis	Few	Cor pulmonale; cirrhosis.
H	Fibrosis	Very many	Proliferative glomerulonephritis, Fasciola in liver.
J	Fibrosis/cell influx	Many	Lungs only examined.
K	Fibrosis	Many	Fasciola in liver.

Table (15). Diffuse fibrosing alveolitis: significant lesions at postmortem in ten cases of the disease.

EXTRINSIC ALLERGIC ALVEOLITIS OR FARMER'S LUNG IN CATTLE

Two cases of extrinsic allergic alveolitis were encountered and the lesions in the lungs of these cows were comparable to those previously described in this disease of cattle (Pirie et al 1971a; Wiseman et al 1973).

HISTORY

One cow (A) presented with a history of an acute illness in February; she had been found in a dyspnoeic state with tachypnoea and elevated rectal temperature of 105°F. whilst exposed to mouldy hay. There was no history of recent pasture change. The cow was examined and treated by the local veterinary surgeon (treatment included corticosteroids) before referral to us 36 hours later. At this time, the rectal temperature was 101°F. and respiratory rate 40-50 per minute; she aborted shortly after admission. This cow was slaughtered some 80 hours after first being seen to be ill and during this time was not exposed to mouldy hay.

The owner's veterinary surgeon claimed that the second cow (B) was affected by fog fever when she was ill during the winter, and a serum sample revealed the presence of precipitating antibodies to M. faeni at this time. The respiratory condition subsided after treatment (with antibiotics, antihistaminics and corticosteroids) and the owner was unwilling to sell. Later in the season, in July, she aborted and the owner was then agreeable to the sale. Precipitins were still present in the serum.

PATHOLOGY

In cow A, there was an excessive amount of greyish mucus in the trachea and bronchi and many lung lobules were found to be over-inflated, especially at the periphery, and to contain a number of

small grey spots (Figs.71,72,73). There were many fine red spots, apparently haemorrhages, extending over a small part of the lung lobule in all lobes of the lung. Mild interstitial emphysema was noted in the posterior diaphragmatic lobes. Macroscopic lesions were not impressive (Fig. 71).

In cow B, excess, greyish mucus was found in the bronchi and similar material plugged many smaller bronchi and bronchioles in histological sections. A number of grey spots was noted in many lung lobules and many other lobules were overinflated, especially at the periphery. A few lobules were yellowish-white in colour and firm to cut (Fig. 74).

The histological findings were similar in cows A and B and the lesions were multi-focal.

Mucous plugs, sometimes infiltrated by neutrophils, were common and there was a mild exudation of neutrophils and eosinophils into the bronchial lumen. Globule leucocytes were regularly seen in the bronchial epithelium and there were many intra-epithelial neutrophils and eosinophils. Plasma cells and lymphocytes were abundant in the lamina propria, with a small, but constant, proportion of neutrophils. There were many obliterative lesions in the bronchioles and alveolar ducts (Figs.75, 77). Peribronchial plasma and lymphoid cell accumulations were of moderate degree.

In case (A) , there were scattered, focal lesions of alveolar oedema, intra-alveolar haemorrhage and overinflation. Very occasional foci of cuboidal alveolar epithelial hyperplasia or of tall, columnar ciliated cells were found in the alveoli (Fig. 79,80). In many areas there was infiltration and thickening of alveolar septa by plasma cells, lymphocytes and multinucleated giant cells, with increased amounts of collagen and reticulin (Figs. 76, 78). Small numbers of eosinophils

and neutrophils were present in the alveolar septa and in the lumen. Multinucleated giant cells were observed in the alveolar septa (Fig. 78) and in the interlobular lymphatic vessels. Epithelioid granulomata were noted in the alveoli (Figs. 76, 79) and similar lesions were noted in and about the walls of small bronchioles.

There was more intra-alveolar haemorrhage in animal A and in this case also, there were many more haemosiderin containing macrophages in the lung and in the bronchial lymph nodes. Cirrhosis and bilateral pyelonephritis were discovered in animal B.

DISCUSSION

Diffuse fibrosing alveolitis (D.F.A.), which is also known as diffuse interstitial pulmonary fibrosis or the Hamman-Rich syndrome, is a condition of unknown and possibly multiple causation characterised pathologically by a diffuse inflammatory process in the lung beyond the terminal bronchiole, having as its essential features:-

- 1) cellular thickening of the alveolar walls showing a tendency to fibrosis
- and 2) the presence of large mononuclear cells, presumably of alveolar origin, within the alveolar spaces (Scadding and Hinson 1967).

These two essential features are present in varying proportions in different cases and probably at different stages of the same case. There may be other cells in the exudate, fibrin exudation and hyaline membrane formation, fibrotic destruction of lung structure, smooth muscle hypertrophy and proliferation of bronchiolar epithelium to line residual air spaces (Scadding and Hinson 1967). Hyperplasia and metaplasia of alveolar epithelium in D.F.A. were also mentioned by Livingstone et al (1964) and Stack et al (1965). A pulmonary condition in which large mononuclear cells filled the alveolar lumen, without extensive lesions in the alveolar septa, was described by Liebow et al (1965) as "Desquamative Interstitial Pneumonia (D.I.P.)"; this was regarded by Scadding and Hinson as a variant of D.F.A..

The disease was first described by Hamman and Rich (1944) as a rapidly progressive, respiratory syndrome with dyspnoea which was usually fatal within 6 months. The more common manifestation is of insidious onset dyspnoea and cyanosis, leading into cor pulmonale over a much longer period of time (Crofton and Douglas 1969). Since the

original description, there have been many reports and reviews and the disease appears to be becoming more common. The main knowledge of the condition is contained in the reports of Hamman and Rich 1944; Grant et al 1956; Rubin and Lubliner 1957; Scadding 1960; Scadding and Hinson 1967.

The name 'Hamman-Rich syndrome' was applied to this condition for many years, but later the term 'fibrosing alveolitis' was coined by Scadding (1964) and this was then qualified to "diffuse fibrosing alveolitis" (Gough 1964). 'Fibrosing alveolitis' was divided into two groups - "cryptogenic fibrosing alveolitis" a term used to embrace those cases of disease where the cause was not known, and "extrinsic allergic alveolitis" in which the lesions developed as a result of an immunological reaction to an inhaled antigen, such as M. faeni in farmer's lung (Scadding 1967; Pepys 1967). The problems of differential diagnosis of the two forms have been considered. Extrinsic allergic alveolitis was characterised by a typical clinical history and radiological appearance, the presence of serological precipitins to the relevant organic dusts and positive results to inhalation tests with the antigen. Granulomata in alveolar and bronchiolar walls and giant cells were found frequently in the lungs. Cryptogenic fibrosing alveolitis was not associated with granulomata in the lungs and large mononuclear cells were present in the alveoli (Editorial - Lancet 1971).

We have only recently recognised the existence of this type of bovine pulmonary disease in Britain, but in the past 3 years we have examined some 40 cases of diffuse fibrosing alveolitis and a smaller series of cases of bovine extrinsic allergic alveolitis, or farmer's lung. We are only beginning to classify these cases and have become aware of the problems of differential diagnosis between diffuse fibrosing alveolitis and farmer's lung.

The 10 cases of diffuse fibrosing alveolitis described above were characterised by severe, diffuse lesions involving the majority of lobules in all lobes of the lungs. These lesions were cellular infiltration and fibrosis of alveolar septa, accumulation of mononuclear cells in the alveolar lumen, alveolar epithelial hyperplasia and metaplasia, bronchitis and bronchiolitis. Epithelioid granulomata and granulomatous lesions of the walls of small bronchioles were absent. These findings were similar to those of diffuse fibrosing alveolitis of man, although alveolar septal fibrosis was more frequent than mononuclear cell accumulation. We have adopted the nomenclature of the human disease until we have more knowledge of the pathogenesis and aetiology of the condition. One point of difference was the bronchitis and bronchiolitis accompanying the acinar changes in the cow; similar findings have not been emphasised in man, although bronchiolar changes have been recorded (Crofton and Douglas 1969)

Precipitins to M. faeni were present in the sera of 5 of the cases tested. but the significance of this observation is not known. We have found similar precipitins in the sera of many clinically normal cattle and, at the moment, consider such findings only to indicate prior exposure to the organism. The possibility that clinically insignificant, microscopic, pulmonary lesions of farmer's lung were present in these apparently normal animals has not been explored (Pirie et al 1972).

Obliterative lesions in the bronchioles were noted in some animals, including one without precipitins to M. faeni. We have found similar lesions in the lungs of cattle affected by farmer's lung, but we would not consider these to be diagnostic of that disease.

We have recently described an incident of chronic farmer's lung in a herd of cattle, in which the pulmonary lesions were alveolar septal fibrosis and infiltration by plasma and lymphoid cells, with multiple foci of alveolar epithelial hyperplasia. Epithelioid granulomata and giant cells were frequently found and there were granulomatous lesions in the walls of bronchioles with many foci of bronchiolitis obliterans. Precipitins to M. faeni were present in the sera of affected cattle (Wiseman et al 1973).

The diagnosis of bovine farmer's lung was based pathologically on the pulmonary lesions of bronchiolitis, bronchiolitis obliterans, granulomatous lesions in the bronchioles and alveolar ducts, epithelioid granulomata and cellular infiltration of the alveolar septa with fibrosis. The clinical history, serology and results of experimental provocation tests were also consistent with this diagnosis. The lesions in these cattle could be described as diffuse, since they were present in all lobes; because they only involved groups of acini in a proportion of the lung lobules in any lobe, they might better be described as multifocal (Wiseman et al 1973).

Diffuse fibrosing alveolitis was diagnosed in these 10 cattle when :-

- 1) the lesions were diffuse and severe
- 2) the lesions were comparable to fibrosing alveolitis in man
- 3) epithelioid granulomata and granulomatous lesions of the bronchioles were absent.

The diagnosis was made, therefore, irrespective of the presence of precipitins in the sera and without regard to the clinical history; which was not known or was incomplete in many instances. This classification does not deny the possibility that extrinsic allergic alveolitis in the chronic form may reach its terminal stages in the

syndrome of diffuse fibrosing alveolitis in cattle, or that exposure to mouldy hay containing M. faeni was important in the pathogenesis of some or all of the pulmonary lesions in the 10 cows above. It is widely accepted that not all cases of farmer's lung have precipitins to M. faeni in their sera (Pepys 1969) and it is known that the characteristic granulomata may regress after corticosteroid therapy (Dickie and Rankin 1958; Seal et al 1968); it is not known how long the granulomata remain after cessation of exposure. The history of exposure to organic dusts, the clinical signs, radiological appearance and, above all, the symptoms are important in the diagnosis of farmer's lung in man (Crofton and Douglas 1969).

The problems of differential diagnosis of diffuse fibrosing alveolitis and long standing farmer's lung in cattle are more complex, since detailed knowledge of clinical history and signs are rarely available and symptoms are never known. Most cows are exposed to hay and many have precipitins to M. faeni in their sera. Several cows affected by D.F.A. were treated for "pneumonia" some time previous to our examination; it may be that corticosteroid treatment altered the pulmonary lesions.

There are many reasons, therefore, why diffuse fibrosing alveolitis can not be regarded as a distinct entity with one aetiology, although the mechanism by which the lung is damaged may be common to several agents.

At the moment, we would wish to retain 'chronic farmer's lung' or 'chronic extrinsic allergic alveolitis' as a name for pulmonary conditions which have known history, clinical signs and pathology consistent with that disease in man, and to utilise 'diffuse fibrosing alveolitis' to describe the extreme pulmonary condition in which characteristic lesions of farmer's lung are absent, but the lesions

are otherwise similar in nature. It is accepted that in the future it may be possible to show common ground between chronic farmer's lung and some cases of diffuse fibrosing alveolitis in cattle.

A pulmonary condition similar to that described in these 10 cows was recorded by Fankhauser and Luginbuhl (1960) and Luginbuhl (1960 a & b) in Switzerland.

Giesel (1969), in Germany, found similar cases in postmortem examinations of bovine lungs. Mackenzie (1966), in Britain, also detailed 'chronic fog fever' in cattle as a syndrome comparable to that in Switzerland. There is no evidence that "chronic fog fever" exists in Britain. None of the cases of fog fever we examined had pulmonary lesions similar to those of diffuse fibrosing alveolitis and only two animals were said to have been affected twice. The seven animals which were recovered cases did not have lesions of "chronic fog fever" at necropsy. In Switzerland, the epidemiology of 'chronic fog fever' is different from that of fog fever in Britain, since most Swiss cases occurred indoors. There is justification for considering cases of 'chronic fog fever' to be animals with long standing pulmonary conditions, possibly diffuse fibrosing alveolitis or chronic farmer's lung, which have periodic exacerbations of clinical signs, the so called 'fog fever' incidents. This type of acute crisis was frequently treated as 'pneumonia' in several of the cows examined above.

The pulmonary lesions in the 10 cows examined varied greatly in degree and this is consistent with the situation in man (Scadding and Hinson 1967; Livingstone et al 1964). The most severe lesions were found in animals F and E; this latter animal had been moved to fresh pastures each week and the last pasture change was 7 days before the final illness was first noticed. It was admitted that she had been affected by a respiratory illness during the previous winter and had

not recovered fully. We do not know whether the pasture change exacerbated the pulmonary lesions or if "fog fever" was superimposed, since the clinical history was of a longstanding illness and the pulmonary lesions were gross and obviously of long duration in most instances. It appeared more likely that the pasture change was coincidental and that the final deterioration was the result of an oedematous phase, possibly due to cardiac failure.

It is interesting to note that cor pulmonale developed in 3 animals, since this has been described in man as a typical terminal event (Crofton and Douglas 1969), and that lesions in the liver and kidneys were also found. Diffuse fibrosing alveolitis was described in association with chronic liver disease (Turner-Warwick 1968), but the interpretation of the bovine cases is complicated by the presence of bile duct fibrosis and hepatic lesions attributable to Fasciola hepatica.

There was an obvious increase in mast cells in the alveolar septa in cases of diffuse fibrosing alveolitis, although these were not quantitated.

Ehrlich and Westphal (cited by Riley 1959) both observed an abundance of mast cells in 'brown induration of the lung'; the histological lesions in this type of disease have been reported by Heath and Edwards (1959) and Wagenvoort, Heath and Edwards (1964). Recently, Heath et al (1969) quantitated the mast cells in mitral stenosis, one of the conditions in which chronic pulmonary venous hypertension gave rise to 'brown induration'. Elevated mast cell numbers were found in mitral stenosis and this was attributed to chronic exudative changes in the lungs or prolonged excessive pulmonary blood flow. Increased numbers of mast cells were also discovered in the lungs of rats fed on Crotalaria spectabilis seeds (Kay et al 1967), in which pulmonary hypertension was induced by

plant poisons. It was considered that the pulmonary mast cells did not initiate the elevated pulmonary arterial blood pressure by secretion of serotonin, but merely proliferated as part of the chronic exudative changes which developed in the lungs under such dietary conditions. This view was supported by the suggestions of Riley (1959), who claimed mast cell hyperplasia was a secondary phenomenon associated with the laying down of collagen fibres.

The role of mast cells in diffuse fibrosing alveolitis is not known.

THROMBOSIS OF THE POSTERIOR VENA CAVA WITH PULMONARY

THROMBO-EMBOLISM AND HAEMOPTYSIS

THROMBOSIS OF THE POSTERIOR VENA CAVA WITH PULMONARYTHROMBO-EMBOLISM AND HAEMOPTYSIS

Three animals exhibiting acute respiratory signs were found to have a septic thrombus in the posterior vena cava. Septic emboli from this focus were disseminated through the pulmonary arterial branches and had produced pulmonary abscesses and lesions in that vessel.

In each case, a thrombus was found in the posterior vena cava, either in the hepatic portion or in the thoracic part (Figs. 81, 82). Such thrombi formed large, rough-surfaced masses which projected into, and sometimes occluded, the lumen of the vessel. When the thrombus was large and was located anterior to the openings of the hepatic veins, there was marked chronic venous congestion of the liver (Fig. 84). Abscesses were sometimes found beneath the thrombus within the liver substance; absence of an infected focus at the time of postmortem does not preclude the presence of such a lesion previously. Septic emboli, released from the caval thrombus, had given rise to multiple lung abscesses in all lobes and to foci of thrombo-embolism in the branches of the pulmonary artery; valvular endocarditis was not a feature. There were large aneurysms in the pulmonary artery along its major lobar branches. These dilatations of the vessel appeared to have arisen, in many instances, at sites of thrombo-embolism, presumably where the wall was weakened. There were also indications that an aneurysm could develop where an abscess lay between the artery and the bronchial tree since saccular outpouchings of thinned vessel walls were found at such points, in the absence of local thrombo-embolism in the vessel lumen (Fig. 86).

Some aneurysms had ruptured and large volumes of blood, in lamellated clots, were found around the vessel, compressing the pulmonary tissue into a limiting capsule (Fig.85, 87). It was often impossible to trace the course of the apparently obliterated pulmonary artery out of such a ruptured vessel, since the pulmonary structure (Fig.83) was obliterated by massive blood clots, a distorted vessel and, often, multiple lung abscesses or necrotising broncho-pneumonia in the surrounding lobe. Frequently there was haemorrhage into the bronchial tree and large volumes of clotted blood were coughed up or swallowed (Fig. 86), to be found at necropsy in the bronchi, trachea and pharynx or in the oesophagus and rumen. Fatal haemoptysis was occasionally observed. Aspiration of blood from the bronchial tree into the alveoli filled many lung lobules with blood and produced a deep red colour in some segments (Fig. 82), the tissue was otherwise normal.

A series of cases of thrombosis of the posterior vena cava with pulmonary arterial thrombo-embolism has been described by us (Selman et al 1973c in press).

PULMONARY DISEASE DUE TO REINFECTION WITH

DICTYOCAULUS VIVIPARUS

INTRODUCTION

RESULTS

DISCUSSION

PULMONARY DISEASE DUE TO REINFECTION WITH DICTYOCAULUS VIVIPARUSINTRODUCTION

Reinfection husk was diagnosed in 6 animals from 3 outbreaks of respiratory disease in adult cattle. The affected herds were all managed on commercial dairy lines and the six cows were adults of Ayrshire or Friesian breeds. The main clinical signs, which were recorded in the majority of animals in the herd, were coughing and depression of the milk yield, 8-14 days after movement to fresh pasture in August; there were no deaths. In contrast to the beef herds described above in the section dealing with fog fever, the dairy cattle had always been moved from one good sward to another.

The clinical syndrome could be readily distinguished from fog fever and the pathology was also dissimilar. The pulmonary lesions are recorded below, since there is little information in the literature on this type of disease in natural cases.

RESULTS

Pathology The main lesions were confined to the lungs at postmortem and these were of normal size, weight, colour and consistency. Severe pulmonary oedema and interstitial emphysema were not recorded, although there was focal oedema of some lobules and localised interstitial emphysema, with overinflation of many acini, about a few segments of the diaphragmatic lobes in two animals. Small red spots, extending over $\frac{1}{2}$ or less of the lobule, were noted in most lungs; these were areas of congestion, intra-alveolar oedema, haemorrhage and deposition of hyaline material.

The most significant finding was a variable number of pulmonary lymphoid nodules, each up to 3-4mm in diameter, in each lobe

of each lung (Fig. 88). These did not appear to be selectively distributed in any lobe and could be found most easily beneath the visceral pleura. The nodules were raised above the lung surface and usually had a greenish-yellow centre, surrounded by a middle greyish zone and a red periphery (Fig. 89). After section, the greenish centre could be expressed without difficulty. The number of nodules varied greatly, the maximum counted beneath the pleura of both lungs was 30.

Two types of nodule were found microscopically. The largest and most numerous (Figs. 90,91) had a central core of brightly eosinophilic parasitic debris surrounded by very many proliferating macrophages, many multinucleated giant cells and a few bizarre, hyperplastic epithelial cells resembling those of the bronchiolar lining. Immediately external to this was a ring of numerous eosinophils intermixed with macrophages, immature plasma cells, lymphocytes and a few giant cells. A thicker zone of lymphocytes and plasma cells surrounded the lesion and, in some nodules, these were beginning to form aggregates indicating probable germinal centre development. Eosinophils infiltrated all the layers and, in some nodules, many dead and disintegrating eosinophils could be found around the parasitic fragments. This type of nodule was sometimes seen to be in a bronchiole, but in a few instances the site could not be ascertained. The smaller nodule appeared to be an earlier stage of the previous lesion and was less often discovered. The brightly eosinophilic parasitic fragments were more intact and the outline of the larva could be traced. The lung architecture was less distorted and it could be seen that the lesion was in a small bronchiole. The parasite was surrounded by hyperplastic, bronchiolar epithelial cells, which were no longer on the lamina propria, multi-nucleated giant cells and proliferating

macrophages, which thickened the lamina propria. Eosinophils infiltrated the lesion in large numbers and were present in the adjacent connective tissue. Although the normal bronchiolar epithelium had been destroyed, the parasite lay on the lamina propria, which was hypercellular, and the bronchiolar muscle was usually intact. Around the larger nodules, there was commonly an outer ring of congested, oedematous alveoli filled by hyaline deposits, multinucleated giant cells and infiltrated by eosinophils. Fibrin could be found in some of these alveoli.

An excessive volume of greenish mucus was found in the trachea and bronchi and similar material commonly plugged smaller bronchi; in some cases this resulted in a wedge-shaped segment of reddish-brown collapsed alveoli about the plug. This mucus was heavily infiltrated by eosinophils, many of which were disintegrating. Globule leucocytes were frequent in the bronchial epithelium, but the eosinophil was the most numerous cell type in, on and beneath this layer. The epithelium was disrupted and 'tattered' in places as a result of the many migrating cells. A few plasma cells and lymphocytes were also found intra-epithelially but these were infrequent; they were abundant in the lamina propria, around the mucous glands and in the peribronchial connective tissue, where aggregates of cells were formed. Eosinophils were common in the deeper parts of the lamina propria, around the mucous glands and in the peribronchial connective tissue.

Organising intra-bronchiolar exudates were large and very common, in all lungs. Some bronchioles were plugged by a mass of disintegrating eosinophils or mucus and eosinophils and these cells were infiltrating the lamina propria and peribronchiolar connective tissue. The bronchiolar epithelium was often 'tattered' and hyperplastic.

Eosinophils diffusely infiltrated the interlobular septa and formed large aggregates in these sites; this infiltration probably caused the greenish tinge which was noted in many septa macroscopically. Eosinophils also infiltrated the connective tissue in all parts, including perivascular and peribronchial tissue. In a few sections, eosinophils were found in and around pulmonary venules and in the walls of these vessels, but this was not a common observation and was not repeated in all lungs. Granulomatous lesions were also noted in the perivascular connective tissue of one lung; these were focal accumulations of macrophages, multinucleated giant cells and eosinophils, without parasitic fragments.

There were few lesions in the alveoli, apart from those adjacent to nodules. Focal oedema, congestion, intra-alveolar haemorrhage and the formation of hyaline deposits containing fibrin were commonly noted in acini away from nodules, but such lesions were very small. One animal had focal lesions of alveolar epithelial hyperplasia, in addition to those above, involving scattered lobules in all lobes of the lungs. This lesion was not extensive and involved only a small number of lobules. A few small adult worms were found in the bronchi of this animal and obliterative bronchiolar lesions were particularly common.

The bronchial and mediastinal lymph nodes were enlarged and oedematous but gas bullae and haemorrhages were not recorded. There was intense eosinophil infiltration of all parts of the nodes, but these cells were most numerous in the subcapsular sinus, in the trabeculae and in the hilar area around the small blood vessels. Reticular-endothelial hyperplasia and enlargement of the germinal follicles (in which eosinophils were common) were also recorded. Carbon deposits were noted in many nodes.

DISCUSSION

Reinfection husk was mentioned by Jarrett et al (1960) as a syndrome involving the sudden onset of severe and persistent coughing, in a whole herd of cattle, which could sometimes terminate fatally. The condition was associated with the development of pulmonary lymphoid nodules where larvae were destroyed in the lungs. Reinfection husk was attributed to a moderately large number of larvae reaching the lungs, before being killed or expelled, in an animal with waning immunity.

The formation of pulmonary lymphoid nodules was studied in experimental infections with normal and irradiated larvae in calves (Jarrett and Sharp 1963) and they were found in subsequent investigations of the duration of immunity to D. viviparus (Michel and Mackenzie 1965; Pirie et al 1971c).

The clinical signs in these six cattle, the epidemiology and the pulmonary lesions were not those of fog fever in beef cattle, although the presenting feature was acute respiratory signs after a change of pasture in each case.

We have not encountered reinfection husk in beef cattle which presented with clinical and pathological similarity to the outbreaks in dairy herds, nor have such incidents been described in the literature. This may reflect some fundamental difference either in immunity or patterns of exposure between beef and dairy herds.

The duration of immunity to D. viviparus has been studied using vaccinated calves (Michel and Mackenzie 1965; Pirie et al 1971c) and it is clear that there is some loss of immunity in the absence of exposure after vaccination, although the period over which this develops is not agreed.

There have not been parasitological investigations into the pattern of exposure in natural outbreaks of reinfection husk and it is supposed that acquired immunity wanes in a similar manner to that of vaccinates after a period of low or negative challenge and the syndrome develops when a subsequent challenge is "heavy". The duration of immunity in adult cattle has not been studied.

Reinfection husk, in which pulmonary lymphoid nodules are formed, can be distinguished from fog fever clinically and pathologically. Similar nodules also appear in the lungs of animals treated with diethylcarbamazine during lungworm infection, as a result of death of larvae in small bronchioles (Jarrett et al 1962) and this possibility should be considered in routine diagnosis.

ACUTE PULMONARY OEDEMA AND INTERSTITIAL EMPHYSEMA

HISTORY AND PULMONARY PATHOLOGY

DISCUSSION

ACUTE PULMONARY OEDEMA AND INTERSTITIAL EMPHYSEMA

Acute pulmonary oedema and interstitial emphysema were the main findings in two dairy cows which died after a very short illness; details of these cases are recorded below.

ANIMAL (1)

This $3\frac{1}{2}$ year old, Ayrshire cow was almost at the end of its current lactation and was not noticed to be abnormal when it was brought in for milking at 6a.m. Shortly afterwards, at the time of milking, the farmer noticed the cow had ruminal tympany and was breathing very rapidly. The veterinary surgeon attended during the morning and found the cow exhibited gross dyspnoea, severe ruminal tympany, increased frequency of micturition and very fluid diarrhoea. The cow was treated with antihistaminics, but died 30 minutes later. She had been grazing on two fields for about 6 days, neither field was aftermath but both were well grown. The duration of the illness was 2 to 3 hours.

At necropsy, the lungs were remarkably distended as a result of severe interstitial emphysema (3+) involving all lung lobes, with large gas bullae and extensive subpleural gas dissection. Severe interstitial and pulmonary oedema, with dilated interlobular septa filled with gelatinous, yellow oedema fluid, was recorded. Many lung lobules were dark red in colour, congested and oedematous, with a smooth glistening cut surface. The trachea and bronchi were filled by white fluid and the mucosa beneath this was deeply congested and very haemorrhagic. Similar congestion was noted in the turbinates and nasopharynx, but haemorrhages were only observed in the latter. The bronchial and mediastinal lymph nodes were enlarged and oedematous, but gas bullae were absent.

Many epicardial and sub-endocardial petechial haemorrhages were found in the left ventricle and there were petechiae in the kidneys. The udder was very congested. There were no gross lesions in the alimentary tract although the contents were very watery.

Microscopically, severe pulmonary oedema with hyaline membranes and interstitial emphysema were the most significant findings (Figs.92,93).

Precipitated oedema fluid protein and hyaline membranes filled many alveoli and many eosinophils and neutrophils infiltrated the alveolar septa and the luminal contents. Intra-alveolar haemorrhages were common and the alveolar septal capillaries were very congested (Figs. 93 & 94). Red blood corpuscles were found in many alveolar macrophages and these cells were increased in number in the lumen, where there were occasional giant cells. There was oedema of the alveolar and interlobular septa and many eosinophils, sometimes arranged in aggregates, were found in these sites. Eosinophils were commonly found in the lumen, in the alveolar septa and in the connective tissue about small pulmonary venules.

Globule leucocytes were numerous in the bronchial epithelium and eosinophils and neutrophils were often present. Neutrophils and eosinophils infiltrated the precipitated oedema fluid in the bronchial lumina. Eosinophils were common in the oedematous lamina propria, which was also heavily infiltrated by plasma and lymphoid cells. Congestion and haemorrhages were noted in the lamina propria blood vessels. Plugs of eosinophils and hyaline deposits filled some small bronchioles and there were eosinophils and neutrophils in the lamina propria. Interstitial emphysema was noted in many histological sections and many acini were overinflated. Eosinophils were abundant in interlobular lymphatic vessels.

ANIMAL 2.

This $3\frac{1}{2}$ year old Ayrshire cow was near the end of her first lactation and, with the rest of the herd, had been given access to two fields, one of which was aftermath, 5 days before. On 19th August, she was apparently normal at the morning milking, but was seen to be very ill in the afternoon and deteriorated during the walk back to the farm for milking.

The veterinary surgeon found her dull, and dyspnoeic with a marked expiratory grunt, froth at the mouth and severe diarrhoea. The cow was given oxygen but became more dyspnoeic overnight: she was slaughtered in extremis, and the lungs submitted to us.

The lungs were voluminous and severe interstitial emphysema (3+), with large gas bullae and subpleural gas dissection, was apparent. Gelatinous, yellow oedema fluid accompanied the interstitial gas in many sites and there was marked, diffuse, pulmonary oedema. Many lung lobules were dark red, rubbery and, after section, had a smooth glistening surface from which fluid ran freely. Abundant, frothy white oedema fluid was found in the trachea and bronchi and there was some frank blood in smaller bronchi.

Pulmonary oedema and hyaline membranes with interstitial emphysema were the most significant lesions microscopically. Lesions were similar to those noted in Animal 1 except the oedema fluid was more extensive and stained more densely with eosin, and free blood was found in many bronchi.

DISCUSSION

'Milk Allergy' of cattle is a syndrome characterised mainly by urticaria and respiratory distress. Multiple skin swellings, dyspnoea and tachypnoea, which in a minority of cases have a fatal outcome, have been described in cattle, particularly at the end of lactation (Houllier and Dellanoy 1903; Brewer 1957; Mullins 1960).

This condition has recently been investigated in detail (Campbell 1970b) in America and has been shown to be not uncommon, especially in dairy breeds. Since the epidemiology section of the report was based on farmers' replies, it may well be that this was not entirely accurate but Campbell claimed that the condition was most frequently seen during the first 3 lactations, especially towards the end of a lactation. He quoted the opinions of a few farmers who had noticed episodes particularly after a sudden change of pasture to lush grazing. Clinical signs included very fluid diarrhoea, urticaria (often of short duration), increased frequency of micturition and respiratory distress. Deaths were not common but pulmonary oedema was recorded in a fatal case. Campbell attributed the syndrome to a hypersensitivity reaction to the animal's own milk, possibly to α and β -casein, β lactoglobulins and α lactalbumin. When one animal was injected with its own milk, it died rapidly and interstitial emphysema was a prominent lesion in the lungs at necropsy.

Although urticaria was not noticed in the two cows 1 and 2, the other findings were consistent with "milk allergy" as described by Campbell and others. However, we have no other experience of this type of syndrome or its pathology in our survey. We have seen dramatic clinical signs after intravenous administration of milk to cattle but no fatalities occurred (personal observations). The immunological basis for this reaction, if any, remains unknown.

The syndrome described by Campbell has clinical and pathological similarities to anaphylaxis in the bovine (Aitken and Sanford 1969a; Code and Hester 1939), in which pulmonary oedema and interstitial emphysema have been found at postmortem.

The clinical signs in these two cattle were not consistent with a diagnosis of fog fever. The postmortem lesions of pulmonary oedema, interstitial emphysema, hyaline membranes and pulmonary eosinophilia were comparable to some cases of fatal fog fever, but there was more frequent intra-alveolar haemorrhage and a greater degree of pulmonary oedema in these two animals. I have found severe congestion and intra-alveolar haemorrhages to be common in fatal cases of anaphylaxis in the bovine (personal observations). Alveolar epithelial hyperplasia was not a feature in the lungs of these two cows, but this lesion was not found in all fatal cases of fog fever. The pulmonary oedema in case 2 may have been exacerbated by the oxygen therapy.

My clinical colleagues were satisfied that the clinical signs and history of these two animals were not those of fog fever and I would not regard interstitial emphysema, pulmonary oedema and hyaline membranes as being diagnostic of that disease. There is strong circumstantial and factual evidence for considering these two cows to be examples of "milk allergy", but until that syndrome is more clearly defined, in Britain, they should be considered to have 'acute pulmonary oedema and interstitial emphysema', which may be recognised as occurring under unknown circumstances.

Begg and Whiteford (1948) outlined a similar type of syndrome in milking cows; their report has been considered to be a record of fog fever in dairy cattle but some of the cows may have been affected by a "milk allergy" syndrome.

FIELD SURVEY: OTHER PULMONARY DISEASES

A number of dairy cattle with longstanding respiratory conditions were diagnosed as cases of fog fever during acute exacerbations of signs which were not related to pasture changes.

The postmortem diagnoses were:-

Chronic suppurative pneumonia (Fig. 95)	6 cases
Necrotising bronchopneumonia	1 "
Carcinoma involving lung and pleura (Lungs only examined)	1 "
Post-patent husk (these animals were cattle from Jersey recently moved to an infected farm in the west of Scotland)	2 "
Malignant Catarrhal Fever (this animal presented with an acute illness)	1 "

DISCUSSION: RESPIRATORY DISEASE IN ADULT CATTLE

DISCUSSION: RESPIRATORY DISEASE IN ADULT CATTLE

Respiratory disease in cattle is regarded as a major problem in veterinary medicine and is a cause of economic loss to the livestock industry in Britain and abroad. There have been many investigations of the pneumonias of young animals, possibly since these affect many animals in the group and are widespread and common; the main reports are those of Jarrett 1954; 1956, Jarrett et al (1957); Omar (1966); Darbyshire and Roberts (1968); Gourlay and Thomas (1970). Factual knowledge of the pulmonary disorders of adult animals, other than the pneumonias of chronic suppurative type, was sparse and the nomenclature was confusing. One aim of this survey was to investigate the respiratory diseases of adults in a systematic manner and to define these in terms of the clinical signs, epidemiology and pathology.

From the field survey, we were able to identify six major pulmonary syndromes in adult cows; these are differentiated below. There was some evidence of a seventh syndrome also.

The commonest respiratory disease was fog fever, which we found was a sudden onset, respiratory distress condition affecting adult animals of beef-type after a change to better pasture in the autumn. Interstitial emphysema, pulmonary oedema and hyaline membranes and proliferation of the type 2 pneumocytes of the alveolar epithelium were the main lung lesions.

Although diffuse fibrosing alveolitis occasionally presented as an acute illness, it was usually possible, where the history was known, to identify this event as one exacerbation of an otherwise chronic, possibly progressive, respiratory disease. Diffuse fibrosing alveolitis was recognised as a cause of respiratory signs and weight loss in older animals and was characterised by severe, diffuse lesions

in all segments of the lungs. These were : fibrosis of the alveolar interstitium with a variable degree of infiltration of plasma and lymphoid cells; accumulation of large mononuclear cells in the alveolar spaces; metaplasia and hyperplasia of the alveolar epithelial cells. We were not able to associate diffuse fibrosing alveolitis with fog fever, but there were many similarities between diffuse fibrosing alveolitis and chronic farmer's lung in cattle.

Bovine extrinsic allergic alveolitis or farmer's lung was an acute or chronic pulmonary disorder in adult cattle exposed to the dust of mouldy hay. The pulmonary lesions of diffuse infiltration of the alveolar interstitium by lymphocytes and plasma cells, epithelioid granulomata and bronchiolitis obliterans with a degree of alveolar interstitial fibrosis in chronic cases have been described (Pirie et al 1971a; Wiseman et al 1973). The distinctions between fog fever and farmer's lung have also been drawn (Pirie et al 1971b).

Acute respiratory signs were encountered in many animals in dairy herds after a change to fresh pasture; these were found to be the result of reinfection with D. viviparus. Pulmonary nodules were present at postmortem in such cases and the lesions of fog fever were not found. We did not encounter any fatal cases of reinfection in the survey. The respiratory signs and depressed milk yield, which were the prominent clinical findings, may have been the result of the development of lymphoid nodules about the larvae in the lungs.

Thrombosis of the posterior vena cava, in the region of the liver or in the thoracic portion, was associated with multiple thromboembolism of the pulmonary artery and, often, fatal haemoptysis from ruptured pulmonary arterial aneurysms. This syndrome was encountered in several dairy animals and the clinical signs and postmortem lesions have been detailed elsewhere (Selman et al 1973c).

Chronic suppurative pneumonia, manifested as bronchopneumonia, bronchiectasis and lung abscesses, was encountered as a common cause of persistent coughing and weight loss in older animals; some of these were submitted as examples of 'fog fever' during severe exacerbations of the chronic signs. Chronic suppurative pneumonia is a common lesion in cattle routinely examined at postmortem.

The six syndromes outlined above were the major respiratory disease groups. There have been no pathological descriptions of a series of clinical cases of the first five syndromes in the British literature.

The existence of a further, seventh syndrome was indicated by the acute lesions of pulmonary oedema and interstitial emphysema found in two dairy cows which died very quickly after first being seen to be ill. This appeared to be different clinically, epidemiologically and pathologically from fog fever in the two cases examined. Further investigation is needed to ascertain the cause and incidence of this type of respiratory disease, since it seems likely it could be one cause of sudden death in dairy cows and cases could be missed for this reason. Veterinary surgeons often mentioned that 'fog fever' occurred in dairy cattle in their practices, but there were no dairy animals with pulmonary lesions of fog fever in our survey, unless they were suckler cows. It may be that some of these acute signs in dairy cows were the result of reinfection with acute pulmonary oedema and interstitial emphysema, since we have no evidence that fog fever occurs in dairy cattle in milking herds.

Jarrett et al (1954) found that several different syndromes were responsible for the clinical signs in cases of 'fog fever'. It was clear from that report that a great deal of confusion was caused

by the use of the term 'fog fever' solely as a name for pulmonary conditions presenting with signs of severe acute respiratory distress. The results of our survey indicate that these sudden onset respiratory distress conditions in adults may be differentiated clinically, epidemiologically and pathologically. The name 'fog fever' should be restricted to the entity in beef-type cattle described above.

RESPIRATORY DISEASE IN ANIMALS IN THEIR FIRST GRAZING SEASON

RESULTS: PRE-PATENT AND PATENT PARASITIC BRONCHITIS AND PNEUMONIA

RESULTS: POST-PATENT PARASITIC BRONCHITIS AND PNEUMONIA

DISCUSSION

RESPIRATORY DISEASE IN ANIMALS IN THEIR FIRST GRAZING SEASON

Forty four animals in their first grazing season were admitted after a diagnosis of "fog fever" had been made by their owner's veterinary surgeon. In the majority of cases, the clinical diagnosis made by us at the time of admission was parasitic bronchitis, after due consideration of the epidemiology and clinical signs.

The clinical history and epidemiology of these animals will be the subject of a separate communication (Selman et al - to be published). In most cases, the history was of a group of unvaccinated calves grazing pastures previously stocked by older animals; although many animals were usually mildly affected, only a minority were ever severely ill and this latter group were suspected to be cases of "fog fever". The existence of clinical parasitic bronchitis on the farm was often unsuspected, or emphatically denied, by either the veterinary surgeon, the farmer or both. The epidemiology and clinical signs were comparable to those described previously (Jarrett, McIntyre and Urquhart 1953, 1954, 1957 and Jarrett et al 1960) and in most instances, the diagnosis was straightforward, provided the clinical signs and history were known. It was considered that a diagnosis of parasitic bronchitis could have been made initially, on the farm, in the majority of outbreaks and that the diagnosis of fog fever was only made because parasitic disease was not recognised. In a small minority of cases the diagnosis was more difficult, either because the animals had been repeatedly moved from field to field and treated with anthelmintics, or because a recently purchased animal had been mixed with a group of home-bred animals with a different grazing history. Some calves were said to have been

vaccinated with Dictol* lungworm vaccine; there was never any means of confirming this and close questioning often revealed that perhaps only spring born calves were vaccinated, the autumn born animals being left unprotected. Where the administration of vaccine was the responsibility of the farmer, there was no guarantee that storage and dosage were in accordance with the manufacturer's instructions.

The postmortem findings in these calves were consistent with those described by Jarrett, McIntyre and Urquhart (1957) and Jarrett et al (1960) in natural and experimental infections of parasitic bronchitis during the pre-patent and patent stages. However, since the nature and extent of the pulmonary lesions in animals in the post-patent phase have not been completely documented, the postmortem findings in selected cases have been discussed below, since important diagnostic points were raised.

RESULTS: PRE-PATENT AND PATENT PARASITIC BRONCHITIS AND PNEUMONIA

All the calves affected by pre-patent or patent husk were under twelve months old and were admitted between late July and the middle of October. Many breeds, both beef and dairy, were represented in their number. There was not usually a history of recent movement to another pasture and when there was such a history this did not influence the severity of the clinical response. Some significant points in the history of each animal are summarised in table (16).

History The history of one animal is described; this was representative of all the cases in this group.

This animal was an 8 month old, castrated, Friesian cross, male calf, which was one of a group of 40 placed in one field from May to September. Adult cattle and heifers in their second year at grass had grazed the field in the previous season. No animals were vaccinated

* Dictol - oral lungworm vaccine (Allen & Hanbury Ltd).

against lungworms. At the time of examination in August, two calves were dyspnoeic and frequently coughing; the local veterinary surgeon thought they were affected by "fog fever". It was later noticed that many calves in the group were coughing and were tachypnoeic. The farmer recollected that some of the animals were coughing earlier in the season, but considered this was normal. One severely ill calf was examined at postmortem and patent parasitic bronchitis was discovered. Treatment with anthelmintics resulted in abatement of the clinical signs in the remaining animals.

Pathology Four animals were found to be affected by pre-patent parasitic bronchitis and eighteen animals were in the patent phase.

The results of the postmortem examinations are summarised in table (16).

Postmortem findings of eosinophil exudation into small bronchioles, with collapse and consolidation of associated acini; pulmonary oedema and hyaline membranes; interstitial emphysema; focal alveolar epithelial hyperplasia and immature worms present in the bronchial tree were considered to be characteristic of pre-patent husk. The lungs of a case of pre-patent husk are shown in figure (96).

In the patent phase, widespread consolidation of lung lobules, especially along the ventral half of the diaphragmatic lobes; interstitial emphysema; pulmonary oedema and hyaline membranes; focal alveolar epithelial hyperplasia and many adult worms in the trachea and bronchi were observed (Fig. 97).

In each case, the extent of the pulmonary oedema and hyaline membranes and interstitial emphysema probably determined the severity of the clinical response. In 2 of the 4 cases of pre-patent husk and in 8 of the 18 patent cases, the interstitial emphysema and pulmonary oedema was moderately severe (2+) and in 4 of the patent animals it was very severe (3+). Alveolar epithelial hyperplasia was always focal and never involved whole lobes of the lungs.

C A S E	D A T E	A G E	S E X	MAIN PULMONARY LESIONS		LUNGWORMS IN AIRWAYS	DIAGNOSIS
				INTERSTITIAL EMPHYSEMA	PULMONARY OEDEMA		
1	Aug	10m	M	++	+	No adults	Prepatent husk
2	Aug	9m	F	+	+	" "	" "
3	Oct	4m	M	-	+	} Given Nilverm	" "
4	Oct	8m	F	-	-		" "
5	Aug	6m	M	+	+	many	Patent husk
6	Aug	9m	F	++	+	many	" "
7	Sept	6m	M	++	+	100	Late "
8	Sept	6m	M	++	+	many	" "
9	Sept	10m	M	+++	+	350	" "
10	July	6m	F	+++	++	many	" "
11	Aug	12m	F	+	++	many	" "
12	Aug	10m	M	++	+	many	" "
13	Aug	8m	M	++	++	many	" "
14	Aug	4m	F	+++	++	very many	" "
15	Sept	12m	M	+	++	400	" "
16	Sept	12m	M	+	++	100	Late "
17	Sept	12m	M	++	-	Few	Treated "
18	Sept	7m	M	+	-	many	Patent husk
19	Sept	4m	M	+	+	moderate	" "
20	Sept	7m	M	+	++	150	Late "
21	Sept	10m	F	+	+	many	" "
22	Oct	5m	M	++	+	moderate	" "

Table (16). Significant features of the clinical and postmortem findings in 22 cases with acute onset respiratory distress during their first grazing season.

RESULTS; POSTPATENT PARASITIC BRONCHITIS AND PNEUMONIA

In the survey, twenty two cases of post-patent parasitic bronchitis and pneumonia were encountered in animals at grass for the first time. These animals were divided into two groups on the basis of the gross pulmonary lesions:-

Group 1 The pulmonary lesions in this group of 17 calves were considered to be typical of uncomplicated post-patent husk.

Group 2 The pulmonary lesions in this group of 5 calves were almost identical to those found in fog fever in adult beef cattle: this group was representative of complicated post-patent husk.

Significant clinical and postmortem findings in the animals of groups 1 and 2 are summarised in table (17).

Group 1

All the 17 calves in this group were aged 5-12 months, were in their first season at grass and were admitted for examination between September and mid-December, with one exception which was investigated in July. Adult lungworms, from 1 to 150 in number, were found in the trachea and bronchi of 11 animals, along with frequent areas of pulmonary consolidation and alveolar epithelial hyperplasia; animals (2), (3) and (4) are representative of 11 of these calves. No lungworms were detected on gross examination of the trachea and bronchi of 6 calves, but the histological and gross pulmonary lesions were considered typical of uncomplicated post-patent husk; animal (1) is an example of these 6 calves. The history and postmortem findings of animals 1, 2, 3 and 4 are given in more detail in appendix 3.

Three types of lung lesion were commonly found on macroscopic examination, these were :-

- 1) Slightly collapsed, reddish-brown lobules with prominent, thickened, yellow-green bronchioles 'spotting' the cut surface.
- 2) Overinflated acini, which were pale pink in colour and puffy in texture.
- 3) Fawn-brown, rubbery lobules with a smooth, glistening cut surface, from which little fluid or gas could be expressed; these lobules were affected by alveolar epithelial hyperplasia.

The lung lesions in all calves were basically similar and the lesions varied in extent, which was not related to the number of adult worms recovered at autopsy. The worms were found in a variable quantity of thick, yellowish mucous exudate in the bronchial tree. The number of worms recovered ranged from 1-150 in the 11 animals with an obvious parasitic burden. Adult gravid worms or fragments of dead parasites were found in the lungs of the six remaining calves after microscopic examination (a minimum of 20 lung sections was examined in each case).

Areas of consolidation and alveolar epithelial hyperplasia were found in all lobes, but were usually most extensive in the ventral diaphragmatic lobes: there was often a sharp demarcation between affected areas and apparently normal lung. Overinflated acini were most frequent in the dorsal parts of the lobes. Interstitial emphysema and pulmonary oedema were severe in a number of cases. Alveolar epithelial hyperplasia was not the most widespread lesion and never involved more than about one third of any lobe; this restricted distribution and the many consolidated lobules produced a different appearance from the lungs of animals affected by fog fever (the lungs of case 3 are to be seen in Fig. 98).

Histological examination of consolidated lobules indicated that the bronchi and bronchioles were frequently filled by a mass of neutrophils, macrophages, basophilic hyaline debris, small numbers of eosinophils and many effete cells. The bronchial epithelium, which was heavily infiltrated by migrating cells, principally neutrophils, was hyperplastic and 'tattered', with clear spaces between adjacent epithelial cells. Globule leucocytes were very infrequently found in the epithelium. Moderate numbers of neutrophils, eosinophils, plasma and lymphoid cells were observed in the lamina propria. Large, organising, intra-bronchiolar exudates obliterated the lumen of many bronchioles. The alveoli were collapsed, and lined, in many lobules, by a cuboidal, hyperplastic epithelium. Most alveolar spaces contained thick, densely eosinophilic or basophilic hyaline membranes, many macrophages and neutrophils, multinucleated giant cells and lesser numbers of eosinophils. Neutrophils were found commonly in the alveolar and interlobular septa.

Overinflated acini were associated with obliterative lesions or blockage of bronchioles by plugs of neutrophils and cell debris, similar to that found in collapsed lobules.

Alveolar epithelial hyperplasia involved the majority of acini in affected lobules and the epithelial lining of the alveoli was composed of cuboidal epithelial cells, in which mitotic figures were frequently seen. Dense eosinophilic hyaline membranes, macrophages, multinucleated giant cells, small numbers of neutrophils and a few eosinophils were found in the lumen. Alveolar septa were often dilated by oedema and contained increased numbers of cells; these were usually neutrophils and eosinophils, but occasional foci of interstitial cell hyperplasia were noted. The bronchioles in these lobules were generally empty, but occasionally contained hyaline deposits or small numbers of

macrophages. Their epithelium was often 'tattered' and hyperplastic, and the neutrophil infiltration was usually light.

The diagnosis of post-patent parasitic bronchitis was made on the basis of the pulmonary lesions of widespread consolidation with alveolar epithelial hyperplasia, and, in addition, the frequent bronchitis, bronchiolitis and bronchiolitis obliterans observed in histological sections. The obvious parasitic infestation noted in eleven animals and the evidence of parasitic remnants in the remaining six animals was consistent with this diagnosis.

The postmortem lesions in all these calves, even in the absence of any demonstration of parasites, were considered typical of uncomplicated post-patent husk, and no problems of differential diagnosis were present.

Group 2

The history and postmortem findings in the five animals (Nos. 18-22) are set out in appendix 3.

These five animals were aged 6-9 months, were in their first season at grass and were examined between September and November. No adult lungworms were found at postmortem and the main pulmonary lesion was diffuse, severe, alveolar epithelial hyperplasia, which involved the majority of lobules in all lobes. The lungs were fawn-brown in colour, very firm and rubbery in consistency and contained little air (Figs. 99,100). Apparently normal segments were found, but these were in the minority. In some cases, very occasional collapsed lobules were observed when the lungs were sectioned (Fig.101). The bronchial tree was usually clean, but small amounts of whitish froth were noted infrequently. Despite the predominance of alveolar epithelial hyperplasia in most sections, there were occasionally other lesions; these were bronchitis,

bronchiolitis, bronchiolitis obliterans, hyperplasia and 'tattering' of the bronchial and bronchiolar epithelium, and blockage of the bronchiolar lumen by plugs of neutrophils, basophilic hyaline deposits and cell debris. Hyaline membranes and pulmonary oedema were recorded in some acini. Occasional saccular dilatations of bronchioles were found; these were areas in which the muscle coat of a segment of the bronchiolar wall was reduced or absent, so that the epithelium and lamina propria bulged through the defect, resulting in the distal airway being wider than the proximal. The epithelium, in the protruding part, was reduced to a cuboidal cell layer or had undergone 'squamous metaplasia'. The underlying lamina propria was heavily infiltrated by plasma cells and lymphocytes at such sites. Globule leucocytes were frequently found at all levels of the bronchial tree, in most cases.

Baermann examination of the lungs of animals 20, 21 and 22 did not reveal any parasites. Adult gravid worms or fragments of dead parasites were found in a number of histological sections from animals 18, 19 and 22. Only a few eosinophilic, homogenous bodies, which may have been portions of dead parasites, were found in the lungs of calves 20 and 21, even though 50-60 lung sections were examined histologically.

ANIMAL	AGE	SEX	MONTH EXAMINED	CONSOLIDATED LOBULES	DIFFUSE ALVEOLAR EPITHELIAL HYPERPLASIA	ADULT LUNGWORMS PRESENT
1	6m	F	Nov.	Yes	Yes	No
2	8m	M	Dec.	Yes	Yes	1
3	6m	F	Sept.	Yes	Yes	7
4	10m	M	Oct.	Yes	No	150
5	6m	M	Dec.	Yes	No	No
6	12m	F	Oct.	Yes	No	No
7	10m	M	Sept.	Yes	No	Few
8	7m	M	Sept.	Yes	Yes	12
9	12m	M	Dec.	Yes	No	Few
10	12m	M	Dec.	Yes	No	Few
11	12m	M	Dec.	Yes	No	Few
12	8m	M	Dec.	Yes	No	1
13	5m	M	July	Yes	No	100
14	8m	M	Oct.	Yes	No	No
15	8m	M	Nov.	Yes	No	No
16	10m	M	Oct.	Yes	Yes	No
17	9m	M	Dec.	Yes	No	No
18	6m	M	Nov.	One Focus	Yes	No
19	9m	F	Nov.	No	Yes	No
20	9m	M	Nov.	No	Yes	No
21	9m	M	Nov.	No	Yes	No
22	9m	F	Sept.	No	Yes	No

Table (17). Significant clinical, pathological and parasitological findings in 22 cases of post-patent patent parasitic bronchitis and pneumonia. The number of adult lungworms found after macroscopic examination of the bronchial tree is given in each case.

DISCUSSION

Exacerbation of the clinical signs during the post-patent phase of parasitic bronchitis (days 55-70 after infection) has been described in natural and experimental infections with this parasite in cattle. These acute, and often fatal, relapses were attributed to complicating pulmonary lesions, principally alveolar epithelial hyperplasia, which developed during the period of expulsion of the parasitic burden from the bronchial tree (Jarrett, McIntyre and Urquhart 1957; Jarrett et al 1960). The pulmonary lesions at this stage of infection were alveolar epithelialisation involving whole lobes, peribronchial fibrosis, intra-bronchial granulomatous polyps and bronchiectasis, in addition to residual lesions of the earlier phases. These lesions were sometimes found in the absence of demonstrable nematodes in the lungs, or when the number of worms was much reduced from that in the patent phase (Jarrett, McIntyre and Urquhart 1957, Jarrett et al 1957 and 1960).

The pulmonary pathology of all the animals of Group 1 was compatible with a diagnosis of post-patent husk based on the criteria outlined above; the parasitological findings were also consistent. The lungs of the calves in Group 2 were very extensively affected by alveolar epithelial hyperplasia, whereas the bronchial lesions were less frequent and less florid than those of Group 1. In Group 2, the lung lesions were so similar to those of fog fever that differential diagnosis was only possible after extensive histological examination.

Alveolar epithelial hyperplasia extending through "all of the anterior lobes and the anterior strips of the diaphragmatic lobes" was found in field cases of post-patent husk (Jarrett et al 1954), although the precise distribution of the lesion in experimental cases of husk was not stated (Jarrett, McIntyre and Urquhart 1957). Extensive alveolar

epithelial hyperplasia was only once found "in the absence of all traces of lungworms" (Jarrett et al 1954) and this was in a case of fog fever. In our series of fog fever cases, there were no significant parasitological findings in the lungs and bronchiolitis obliterans, when present, was very infrequent and confined to the apical lobes.

In animals 18, 19, 21 and 22 of Group 2, the bronchial and bronchiolar lesions, which were noted in several sections and the fragments of parasites in 18, 19 and 22 were considered to be significant traces of lungworm infection, despite the claim that animal 21 had been vaccinated. Post-patent parasitic bronchitis was diagnosed in these animals, on the basis of the pathology and history.

Bronchial lesions were very infrequent in animal 20 and while it may be that further search would have revealed more lesions, it would be impossible to confidently attribute diagnostic significance to these when they were so uncommon. Minimal bronchial lesions were found in the post-patent phase of experimental parasitic bronchitis when there was severe, concurrent, alveolar epithelialisation (Jarrett, McIntyre & Urquhart 1957). A thorough search must be made to identify any collapsed lobules in the substance of the lungs. When there are few or no bronchial and bronchiolar lesions in a large number of sections, it is not possible to confidently distinguish some cases of post-patent husk from cases of fog fever on histopathological grounds alone.

The diagnosis of post-patent husk may be easily made, in some instances, on the basis of the pulmonary pathology, as in Group 1, but in others, it can only be made after consideration of the history, clinical findings and postmortem lesions in each animal.

Globule leucocytes have not been described in parasitic bronchitis, whereas they are numerous in the bronchial tree in cases of fog fever. However, globule leucocytes were found in some of the

cases of post-patent husk, albeit in small numbers, so the presence of this cell type cannot be used to differentiate between these two syndromes, although the numbers may prove to be a useful guide.

The presence of some bronchial lesions in animal 20 and the history of parasitic problems on this farm are suggestive of husk. On the other hand, the history of vaccination, the recent move to better pasture, the many globule leucocytes in the bronchial tree and the absence of any history of recent illness all point to a 'fog fever-like' syndrome.

While one may believe a farmer who claims that none of his calves have been vaccinated with 'Dictol', it is as well to be sceptical of claims to have dosed all of a large number, especially when batches of calves have been mixed. In the case of animal 20, there were 50 Aberdeen Angus-type calves in the group and there was no formal evidence that all had been dosed; the farmer relied on his memory. If this calf had been vaccinated successfully, the bronchial lesions could have been residual lesions, the product of a few irradiated larvae migrating in the lungs, and the extensive epithelial hyperplasia must then have been the result of a 'fog fever' syndrome. However, this calf was the only one affected; we slaughtered two calves, from the same group, a week later and there were no significant pulmonary lesions in these animals, nor were there any 'vaccination nodules'. It is possible, therefore, that calf 20 did not have vaccine protection and, since there was a husk problem on this farm, it was affected by husk. Other animals affected by post-patent husk in this survey were said to have been vaccinated (e.g. animal 21); there was never any corroboration of this claim. Animal 4 had almost certainly been vaccinated; it was thought to be an example of "vaccine breakdown". This probably arose because there was little or no early natural challenge to reinforce the vaccination and

the protection was reduced over the summer. This loss of immunity may be the reason for other apparent failures of vaccination but most cases in this survey were probably the result of the odd animal not receiving vaccine at all.

Animal 20 was the only calf in group 2 which had been moved to better pasture recently, the others were all moved indoors. This may be coincidental, since some calves in group 1 were moved to fresh pasture and the pathology in these cases was different from fog fever.

Globule leucocytes were more numerous in the bronchial epithelium of this animal (20) than in other cases of post-patent husk. Globule leucocytes were often difficult to find and this appeared to be the result of the extreme 'tattering' and hyperplasia of the epithelium. It is possible that globule leucocytes were obvious in animal 20 because the bronchial lesions were less pronounced.

Post-patent husk with severe alveolar epithelial hyperplasia was said to develop in 25% of animals "which were severely affected" in the patent phase (Jarrett et al 1960). It is not recorded whether post-patent husk with extensive alveolar epithelial hyperplasia occurs in calves with few or no clinical signs in the patent phase. It was surprising that there was no history of recent illness in animal 20, in view of the findings of Jarrett et al (1960). In fact, none of the 22 calves were reported as exhibiting clinical signs other than occasional coughing during the summer. This opinion was only that of the farmer and proper examination by a veterinary surgeon may well have revealed otherwise.

Animal 20 could be considered as a case of post-patent husk in a single unvaccinated animal on a farm with a lungworm problem. Alternatively, it could have had a 'fog fever-like' syndrome, but it would then be the only animal in this age group, and the only male

animal, so affected. Since there were many unknown factors in the history, animal 20 has been classified as an extreme form of complicated post-patent husk. Further cases of this type of disease must be investigated, to determine whether this classification is justifiable.

The epidemiology of post-patent husk has not yet been investigated in full, and, although it is known that expulsion of the adult worm burden occurs at this stage, the mechanism by which this is brought about is unknown. Marked epithelialisation has been observed in experimental (Jarrett, McIntyre and Urquhart 1957) and field cases of post-patent husk (Jarrett et al 1954) and the most extensive distribution of this lesion appeared to be recorded by those authors in the latter. We have observed that a change of pasture often precedes the outbreak of post-patent husk, although the time of onset after movement was very varied. Experimental work with Haemonchus contortus in the sheep has shown that a change of grazing to worm free pastures is capable of inducing a self-cure and this reaction has been attributed to herbage alone (Allonby 1972 - personal communication). It may be that a similar change of diet may influence or exacerbate the course of the self-cure in D. viviparus infection and this possibility has not been explored.

"Fog fever" in calves during their first grazing season was found to be probably non-existent. Twenty two of the forty four cases submitted were found to be affected by pre-patent or patent husk. Only 5 of the twenty two cases of post-patent husk presented any difficulties in diagnosis; four of these were diagnosed on history and postmortem findings but in one case there was insufficient data to be certain of the cause.

RESPIRATORY DISEASE IN ANIMALS IN THEIR SECOND GRAZING SEASON

INTRODUCTION

RESULTS

DISCUSSION

RESPIRATORY DISEASE IN ANIMALS IN THEIR SECOND GRAZING SEASON

INTRODUCTION

Six animals aged 14-18 months were referred to us as examples of fog fever; all were in their second grazing season and were examined in September or October. Three were found to have a history and postmortem lesions comparable to those found in group 1 of the younger animals (in their first grazing season). Uncomplicated post-patent parasitic bronchitis and pneumonia was diagnosed in these three and the lesions did not resemble those of fog fever.

Three animals, with complicated post-patent parasitic bronchitis and pneumonia, were found to have gross pulmonary lesions comparable to those of fog fever and the details of these are discussed below. The history and postmortem findings in each case are recorded in appendix 4.

RESULTS

ANIMAL A

Although the main lesion was alveolar epithelial hyperplasia, bronchiolitis, bronchiolitis obliterans and parasitic fragments were frequently discovered. These findings were considered to be consistent with complicated post-patent parasitic bronchitis and pneumonia.

The history supports this view. The episodes of coughing in the heifers, 2-3 weeks after the first pasture change in early September, indicate that the cattle were probably exposed to infective lungworm larvae during their last days on the old pasture or immediately they began to graze the new field. Acute exacerbations, 55-60 days after the move, are consistent with the post-patent phase

of such an infection. The affected heifers changed pastures for the last time about 26 days before becoming ill; this interval is much longer than we have found in cases of fog fever.

ANIMAL B

No parasites were found in the lungs of this animal, but the postmortem findings were otherwise very similar to those found in case A. Complicated post-patent husk was the most likely cause; the history and pulmonary lesions of bronchitis, bronchiolitis and bronchiolitis obliterans were consistent with this diagnosis.

The main change of pasture was 28-42 days before disease was noticed, although there had been a minor change 14 days previously. This calf was the only animal severely ill, although several others were coughing. Problems with lungworm infestations had been regularly encountered on this farm and no animals had been treated in the current year.

ANIMAL C

The congestion, pulmonary oedema and hyaline membranes, interstitial emphysema and alveolar epithelial hyperplasia were very like the lesions found in some fatal cases of fog fever. There was sloughing of the bronchial and bronchiolar epithelium and it was difficult to identify lesions, although bronchiolitis and bronchitis were certainly present. It was not possible to come to a definite diagnosis on the basis of the pulmonary lesions alone.

The history of this animal was not that of classical fog fever. This heifer was taken indoors the day before death and no abnormalities were noticed at that time. None of the cases of fog fever we examined developed inside, whereas several outbreaks of post-patent husk were

noted in recently housed cattle. There was no history of movement to better pasture and the herd had, on the contrary, been scavenging for the greater part of the month. We have, however, encountered a few cases of fog fever apparently developing in animals feeding on turnip tops and rape; in this respect the last week of the grazing history of this animal may be significant.

The known history and postmortem findings are not sufficient to clearly differentiate between post-patent husk and 'fog fever' in this animal.

DISCUSSION

The lung lesions in these six older animals were comparable to those of the two groups, 1 and 2, in the younger grazing calves and three cases raised similar problems of differential diagnosis.

Obvious disease in animals A, B and C began in the period after movement, although the interval varied. The pulmonary lesions in animal C were so extensive that they must have begun before the animal was moved indoors. None of the farmers had noticed any respiratory abnormality in these cattle before the final illness; professional examination would most likely have shown otherwise. Any severe illness should have been obvious even to lay persons, but there was no indication that these animals were adequately supervised.

Animal A had been treated with 'Nemicide'* about 28 days after the pasture change. In experimental infections, when this drug was given to animals in the pre-patent phase of parasitic bronchitis (day 14) the lungworm larvae were destroyed and the lesions suppressed; when animals in the patent stage (day 27) were dosed, there was little change in the lung lesions and not all the worms were eliminated (Urquhart et al 1973 - personal communication). These results suggested

* Nemicide - levamisole hydrochloride (I.C.I.)

that the patent infection was probably not overcome in this case at the end of September. It is not known whether post-patent husk with extensive alveolar epithelial hyperplasia may develop after the adult worm burden has been partially or wholly removed by anthelmintics.

Some adult worms may always remain after treatment with anthelmintics in the patent phase; the burden may never be 'wholly' removed by this process.

The history of animal C strongly suggested that complicated post-patent husk was the cause of the respiratory signs. The results of the investigation illustrated that only a complete history was sufficient for differential diagnosis in a small proportion of cases, where the postmortem findings were not helpful.

Fog fever and post-patent husk have been considered above (see fog fever - discussion). About 75% of cases of post-patent husk (uncomplicated) present no difficulty in diagnosis at postmortem. The other 25% of animals have lesions comparable to those of fog fever; most of these have bronchial and bronchiolar lesions, which may only be discovered after extensive histological examination, and a clinical history consistent with post-patent husk. In a very few cases, in this survey 2 out of 28 (animal 20, appendix 3; animal C, appendix 4), the history and pathology may be insufficient to establish a diagnosis. Such a case is best regarded as one of complicated post-patent husk until it is clearly demonstrated to be otherwise.

RESPIRATORY DISEASE IN ANIMALS HOUSED INDOORS

RESPIRATORY DISEASE IN ANIMALS HOUSED INDOORS

INTRODUCTION

Thirteen animals were referred to us for further examination after developing acute onset respiratory distress with dyspnoea; this was often fatal, despite rapid and varied treatment.

The animals were reared under differing systems of husbandry and were housed indoors at the time the clinical signs developed. All the calves except one (No. 5) had been kept indoors since birth.

Seven animals (Nos. 7-13) were noticed to be ill after receiving the first or second dose of 'Dictol', and this vaccine was blamed for the onset of clinical disease by the owner or his veterinary surgeon.

Animals 1-6 were not vaccinated against lungworms.

Case 5 was submitted to us as an example of 'fog fever' in an indoor calf. When the farmer was questioned he recollected that the animal had been at grass until the late autumn, when it was put with a group of indoor reared calves. The grazing history had been forgotten or ignored in the initial differential diagnosis; the signs were the result of post-patent parasitic bronchitis. Other cases with a similar history were encountered and case 5 has been included as an example of post-patent parasitic bronchitis in the recently housed calf.

RESULTS

A summary of the main findings at postmortem of each case is given in table (18) and, in more detail, in appendix (5).

Four of the five animals of the unvaccinated group (1,2,3 and 6) were found to have a pulmonary disease characterised by

interstitial emphysema, pulmonary oedema and hyaline membranes and alveolar epithelial hyperplasia; a concurrent bronchopneumonia was noted in animals 1, 2 and 3 (Figs. 102, 103, 104, 105).

Calf 5, which had recently been moved indoors, had a clinical history, epidemiology and postmortem lesions typical of post-patent parasitic bronchitis. The postmortem findings were pulmonary oedema and hyaline membranes; alveolar epithelial hyperplasia; marked bronchitis, bronchiolitis and bronchiolitis obliterans.

Interstitial emphysema, pulmonary oedema and hyaline membranes, and alveolar epithelial hyperplasia were observed in three vaccinated animals (8, 10 and 12). The lesions (Figs. 106, 107) were less extensive and florid than in animals 1, 2, 3 and 6. The veterinary surgeon recognised that animal 10 was affected by a severe "proliferative pneumonia" involving apical, cardiac and ventral diaphragmatic lobes, but did not submit samples of this for examination.

Some pulmonary oedema with fine hyaline membranes was noted in animals 7 and 9, but the main lesions in these animals, and in 4, 8 and 11, were those of a simple bronchopneumonia. Pulmonary lymphoid nodules, the result of vaccination, were found in cases 7 and 13.

No inclusion bodies were seen in eosin-phloxine-tartrazine stained sections of bronchus and alveoli from each case.

Bacteriological findings in each case are set out in table (19).

DISCUSSION

Omar and Kinch (1966) described outbreaks of "atypical interstitial pneumonia (A.I.P.)", in indoor calves, in which pulmonary oedema and hyaline membranes, interstitial emphysema and alveolar epithelial hyperplasia were the main lesions at postmortem.

Animals 2-6 months old were affected and the disease was often fatal. The aetiology was unknown.

Animals 1, 2, 3, 6, 10 and 12 had pulmonary pathology consistent with A.I.P.. In every case the epidemiology was different from that of fog fever: the use of the name 'indoor fog fever' to describe this type of incident is misleading and the name is a contradiction in terms. 'Atypical interstitial pneumonia' would seem to be a more useful term until the aetiology is known, but Jarrett (1956) has pointed out that this type of pneumonia is as common as the 'typical' type. That criticism is still valid, but it would be divisive and confusing to put forward yet another name at this stage, without any further understanding of the aetiology.

Animals 10 and 12 were found to have pulmonary lesions of A.I.P.; both had received two doses of vaccine. In neither case was the whole lung examined, only fixed material selected by the veterinary surgeon. The existence of another pulmonary lesion was recognised in animal 10. In this case, and possibly animal 12, the samples submitted were not representative of the pulmonary lesions.

Four of the six vaccinated animals (7, 8, 9 and 11) were mainly affected by a longstanding bronchopneumonia. A large pulmonary abscess was discovered in animal 13. Pulmonary lymphoid nodules, attributed to the first vaccination dose, were seen in animals 7 and 13. The pulmonary eosinophilia, intra-alveolar exudates, hyaline membranes and alveolar epithelial proliferation in animal 7 could have been the result of larvae of either vaccination dose (Jarrett and Sharp 1963); these may have exacerbated the clinical signs of bronchopneumonia. Focal lesions in the diaphragmatic lobe of animal 8 were probably the result of lungworm vaccination and may have produced some clinical signs.

Pulmonary disease after administration of 'Dictol' had been recognised since the vaccine was first developed (Jarrett 1969; McIntyre 1973) and users are warned against dosing animals with clinical respiratory disease.

Clinical signs, of unknown aetiology, have been described several times in association with vaccination (Watkinson 1969; Bown 1969; Cullinane 1969; Martin 1969), but there is little published information on the postmortem findings in such cases.

The results of this small series indicated that some cases of 'post-vaccination' respiratory distress were probably the result of the addition of pulmonary signs, due to larval challenge, to a severe pre-existing respiratory disorder. Most cases of 'vaccination reaction' could probably be explained in this way. In a small minority of animals, the administration of vaccine was not coincidental and the severe respiratory signs were attributed to the vaccine (McIntyre 1973). The aetiology of this reaction is not known. I do not consider that the reports of Watkinson (1969), Bown (1969) and Cullinane (1969) necessarily record such incidents: Martin (1969) has considered these outbreaks in the whole context of calf pneumonia, and pointed out the lack of accurate data.

ANIMAL	AGE	PULMONARY LESIONS					USE OF DICTOL VACCINE	DIAGNOSIS
		INTERSTITIAL EMPHYSEMA	PULMONARY OEDEMA	HYALINE MEMBRANES	ALVEOLAR EPITHELIAL HYPERPLASIA	OTHERS		
1	5m	++	++	++	++	Broncho pneumonia	No	Atypical Interstitial Pneumonia (A.I.P.)
2	4m	+++	++	+	++	"	No	"
3	4m	+++	++	++	+	"	No	"
4	6m	+++	-	-	-	"	No	Purulent broncho- pneumonia
5	6m	-	++	++	+++	Bronchiolitis obliterans	No	Post-patent parasitic bronchitis
6	3m	+	++	++	+++	-	No	A.I.P.
7	6m	+	-	+	-	Broncho- pneumonia	2 doses	'Cuffing' and broncho-pneumonia
8	4m	+	+	+	+	"	1 dose	Broncho-pneumonia
9	6m	++	++	+	-	"	1 dose	Broncho-pneumonia
10	6m	++	++	++	+	'Proliferative pneumonia'	2 doses	A.I.P.
11	6m	+	-	-	-	Aspergillus	1 dose	Broncho-pneumonia
12	+	++	++	+	+	-	2 doses	A.I.P.
13	5m	+	-	-	-	Large abscess	1 dose	pulmonary abscesses

Table (18) Significant clinical and postmortem findings in 13 housed calves affected by acute respiratory distress.

ANIMAL	ORGANISMS ISOLATED FROM BRONCHIAL SWABS
1	No growth
2	A coagulase +ve <u>Staphylococcus</u>
3	A <u>Streptococcus</u> and a Diphtheroid
4	<u>Corynebacterium pyogenes</u>
5	No growth
6	No growth
7	No growth
8	No growth
9	No significant findings
10	No growth
11	Not done
12	Not done
13	<u>Corynebacterium pyogenes</u>

Table (19) Organisms found in bronchial swabs taken from 13 calves developing acute respiratory distress indoors.

DISCUSSION: RESPIRATORY DISEASE IN YOUNGER CATTLE

Parasitic bronchitis was the only diagnosis in animals in their first or second grazing season. In two of the cattle, there were some indications that another syndrome, comparable to fog fever, was involved, but this would have to be established by a further, detailed, specific investigation. We have found that fog fever in adults occurs under very specific conditions, in the autumn and is associated with characteristic pulmonary lesions: the term fog fever should be reserved for this entity alone. There may be occasions when an animal under two years of age is discovered to have clinical signs, history and pulmonary pathology consistent with fog fever. Until the aetiology of fog fever is known, for clarity and to make progress in defining the cause, it is essential that it is not continually confused with other respiratory diseases. There is a need for another term to describe these incidents of sudden onset respiratory distress in other classes of stock. The 'respiratory distress syndrome' might be useful and would include all cases with a history of sudden onset of dyspnoea, of unknown aetiology, with pulmonary lesions of oedema, hyaline membranes, interstitial emphysema and alveolar epithelial hyperplasia. A diagnosis of 'respiratory distress syndrome' would imply that the aetiology was not known. A diagnosis of 'fog fever' in a younger animal would mean that the disease had the same cause as fog fever in adults; this is not known to be the case.

The fact that all these cases in younger animals at grass were diagnosed as 'fog fever' should not be overlooked, for the implication was that the aetiology was unknown. In fact, parasitic bronchitis was responsible and methods for the control of this disease, by vaccination and anthelmintics, have been known for many years. This is the most important result of the investigation of younger grazing animals.

Two significant observations may be made about the indoor calves. The first is that cases of parasitic bronchitis may be overlooked and the second that the respiratory distress syndrome may be encountered.

EXPERIMENTAL RESULTS

CYTOLOGY OF THE ALVEOLAR WALL

1. NORMAL CATTLE

2. FOG FEVER

FOG FEVER: PROVOCATION TESTS WITH DICTYOCAULUS VIVIPARUS

PULMONARY DISEASE INDUCED BY TRYPTOPHAN, 3-METHYL INDOLE AND INDOLEACETIC ACID

ACUTE RESPIRATORY DISTRESS AND BORDETELLA PERTUSSIS

CYTOLOGY OF THE ALVEOLAR WALL

THE ALVEOLAR WALL IN NORMAL CATTLE

1. Introduction
2. Nomenclature of cellular elements of the alveolar wall
of mammals
3. The structure of the bovine lung
4. Results of a study of the fine structure of the alveolar
wall in normal cattle
5. Discussion

THE ALVEOLAR WALL IN FOG FEVER

1. Introduction
2. Histochemistry
3. Ultrastructure
4. Discussion

THE ALVEOLAR WALL IN NORMAL CATTLE

INTRODUCTION

The structure of the alveolar wall has been the subject of considerable discussion for a very long time, but the more detailed morphology has only been satisfactorily elucidated in the last 20 years. The alveolar cells have been identified with the electron microscope but many aspects of the function, inter-relationship and dynamics of these cells remain unknown.

Few investigations of the fine structure of bovine lungs have been made, a surprising observation in view of the high incidence of respiratory disease in this species. It was obvious that existing knowledge was inadequate for future studies of the bovine lung in disease, so the present study was initiated.

Normal tissues were obtained from 10 cattle, 6-12 months of age, which had been reared indoors since birth. These animals were not affected by pneumonia at the time of tissue collection and had no experience of parasitic bronchitis.

The histopathological and electron microscopical techniques were detailed in the general materials and methods section above.

NOMENCLATURE OF CELLULAR ELEMENTS OF THE ALVEOLAR WALL OF MAMMALS

In the latter part of the 17th Century, Malpighi and also Leeuwenhoek used the light microscope to examine lungs and saw the pulmonary blood capillaries. The possibility that these were covered by a surface epithelium was the subject of considerable controversy for many years (Macklin 1938, 1954; Miller 1947; Bertalanffy 1965) and the argument was only resolved with the electron microscope, when Low and Daniels (1952) demonstrated the continuous epithelial lining of the rat lung. In the three hundred years since Malpighi, a confusing nomenclature for the cells of the lung has arisen in the literature, based on different ideas of origin, morphology or function. Meyrick and Reid (1970) reviewed some current concepts of the structure of the alveolar wall of mammals and distinguished three epithelial cells in the surface lining layer and a free cell, the alveolar macrophage, in the alveolar spaces. The three epithelial cells were referred to as the types 1, 2 or 3 pneumonocytes. but earlier workers have given many other names to these cells and these are discussed below. Beneath the epithelial cells, the alveolar wall has been found to contain capillaries, connective tissue fibres and cells and mononuclear interstitial cells, some of which give rise to alveolar macrophages.

The type 1 pneumonocyte is the large, flat cell which covers much of the alveolar surface. Only nuclei are visible with the light microscope since the cytoplasm does not stain by any known selective method. Addison (1842) claimed to see such a cell in the bovine lung, but the first convincing description is that of Low and Daniels (1952) in the rat. This cell has also been known as the membranous pneumonocyte (Macklin 1954), the septal or small alveolar cell (Policard et al 1954 and 1959), type A cell (Yasudo 1958), type 1 cell (Campiche 1960) and pulmonary

surface epithelial cell (Bertalanffy 1965).

Reinhardt (1847) distinguished two epithelial cells, one was cuboidal and resembled that subsequently defined with the electron microscope by Policard et al (1954 and 1959), Schlipkoter (1954) and Karrer (1956). This cell has also been given various names, including septal cell (Lang 1925), granular pneumonocyte (Macklin 1954), alveolar or large alveolar cell (Policard et al 1954 and 1959, Bertalanffy 1965) type B cell (Yasudo 1958) and type 2 cell (Campiche 1960).

A type 3 cell has been described by Meyrick and Reid (1968) in the rat. The origin of this epithelial cell is not known.

The varied nomenclature for the lung epithelial cells developed as a consequence of the morphological similarity between the type 2 cell and the alveolar macrophage, the very different origins and functions of these two cells and the difficulty in resolving the cytoplasm of the type 1 cell with the light microscope. The terms 'type 1' and 'type 2', originally suggested by Campiche (1960), are now widely used and any epithelial cells subsequently recognised in various species will be further designated numerically, as was the third pneumonocyte in the rat. The word pneumonocyte is used, usually with type 1 or 2 as a prefix, though it is often shortened to pneumocyte to avoid any implications of histiocytic origin.

By examining the lungs of foetal rats, Suzuki (1966) and O'Hare and Sheridan (1970) demonstrated that the type 1 and 2 cells were endodermal in origin and originated from columnar epithelial cells of the endodermal branches of the bronchial tree. A continuous basement membrane delineated mesodermal and endodermal components in the lungs of foetal rats from day 16-21 of gestation and in the newborn. Evans et al (1973) followed the renewal of alveolar epithelium in rats exposed to nitrogen peroxide (NO_2) gas, when type 2 cells were found to divide and to differentiate

into type 1 cells. These results were used to support the view that type 2 cells were the progenitor cells for type 1 cells in the mechanism of cell renewal of normal alveolar epithelium. This observation has not yet been confirmed by other workers, but could explain the morphogenesis of alveolar epithelial hyperplasia in disease states.

Virchow (1847) identified a phagocytic free cell in the alveolar lumen and this cell was subsequently referred to as the 'dust cell' (von Ins 1876) or 'alveolar phagocyte' (Briscoe 1908). Karrer (1956) introduced the term 'alveolar macrophage'. The origin of all alveolar macrophages is at present unknown. For many years, several authors (see Stuart 1970 'The RE System') believed these macrophages were desquamated type 2 cells which became phagocytic, and others believed they were migratory cells from the blood. Pinkett et al (1966) and Bowden et al (1969) have provided convincing evidence that the majority of, perhaps all, alveolar macrophages are derived ultimately from the same stem cells in the bone marrow that give rise to the blood monocytes. Blood monocytes do not appear to migrate directly into the alveoli but undergo a phase of maturation and multiplication as interstitial cells in the alveolar wall (Bowden et al 1969) before such movement. Alveolar macrophages differ metabolically, particularly with regard to enzyme activity (Oren et al 1963) and possibly immunologically (Mackaness 1971) from other tissue monocytes and this interstitial phase may represent the period in which these differences develop (Bowden et al 1969).

Much attention has been paid to the epithelial cells of the alveolar wall whereas the cells of the interstitium have been virtually ignored. Bowden et al (1969) proposed that the interstitial cells in the wall gave rise to the majority of alveolar macrophages. Interstitial cells have also been known as septal cells (Rhodin 1963) intra-septal cells (Policard et al 1956) and alveolar (septal) cells (Curry et al 1969).

The interstitial cells are commonly referred to as septal cells, but this name has also been used by Lang (1925) to describe type 2 cells of the alveolar epithelium and by Policard et al (1954) for the type 1 cells; it has, therefore, other associations. The term 'interstitial cell' seems more appropriate, but even this may be an oversimplification, in that interstitial cells may yet be shown to have different functions and separate populations may be discovered with the use of more sophisticated techniques. In this case, a numbering system might be employed, as in the surface epithelium.

Curry et al (1969) claimed to have recognised two types of 'alveolar (septal) cell', one of which contained lipid vacuoles, in the interstitium of the mouse lung. This may have confirmed the previous observations of Bertalanffy and Leblond (1953), who had identified two morphologic types of cell (vacuolated and non-vacuolated) in this position with the light microscope.

In an otherwise exhaustive review of the structure of the alveolar wall, Meyrick and Reid (1970) mentioned only fibroblasts and occasional smooth muscle cells in the interstitium, but other connective tissue cells, including mast cells, plasma cells and occasional lymphocytes have also been found in this position (Epling 1964a) and are mentioned in passing by most authors.

The morphological arrangement of the alveolar wall has been explored by Ryan et al (1969) and they found that a capillary network lay on each side of a central connective tissue sheet and there were frequent anastomoses, across the septum, between these capillary beds. This arrangement, it was suggested, provided maximal area for gas diffusion, minimal blood: air barrier and a pathway for extracellular fluid transport.

Surface tension effects in the lung were demonstrated by van Neergaard (1929) and Mellroy (1952). Pattle (1955) postulated secretion,

in the alveoli, of a lining layer capable of reducing surface tension at the alveolar-air interface. Macklin (1954) had hypothesised that the type 2 cell secreted a thin alveolar lining layer and much research since has tried to establish the link between the surface active material, or surfactant, and the type 2 cell.

Considerable controversy surrounds the origin and function of surfactant. It is generally believed that a layer of single molecules of dipalmitoyl lecithin, a phospholipid, is the surfactant and this rests on a water soluble 'hypophase' containing Hale positive mucopolysaccharides, which coats the alveolar epithelial cells of the normal lung (Avery 1962; Scarpelli 1968; Kikkawa et al 1970). Some workers believe that dipalmitoyl lecithin originates in type 2 pneumocytes (Heinemann 1968; Kuhn 1968; Goldenberg et al 1969; Askin and Kuhn 1971) and others that the Clara cells of the bronchioles are the source (Niden 1967; Etherton et al 1973). Both groups may be correct since both bronchioles and alveoli are said to require surfactants to ensure their stability during the pressure fluctuations of breathing (Macklem et al 1970; Gil and Weibel 1971).

The surfactant layer has not been satisfactorily demonstrated in tissue sections prepared using osmium tetroxide or glutaraldehyde fixation since dipalmitoyl lecithin, a saturated phospholipid, is not fixed by these methods and is removed by the alcohol during processing.

Dermer (1969, 1970) claims to have shown such a lining layer in the lungs of rats and other small animals by adopting a tricomplex flocculation technique using lead salts.

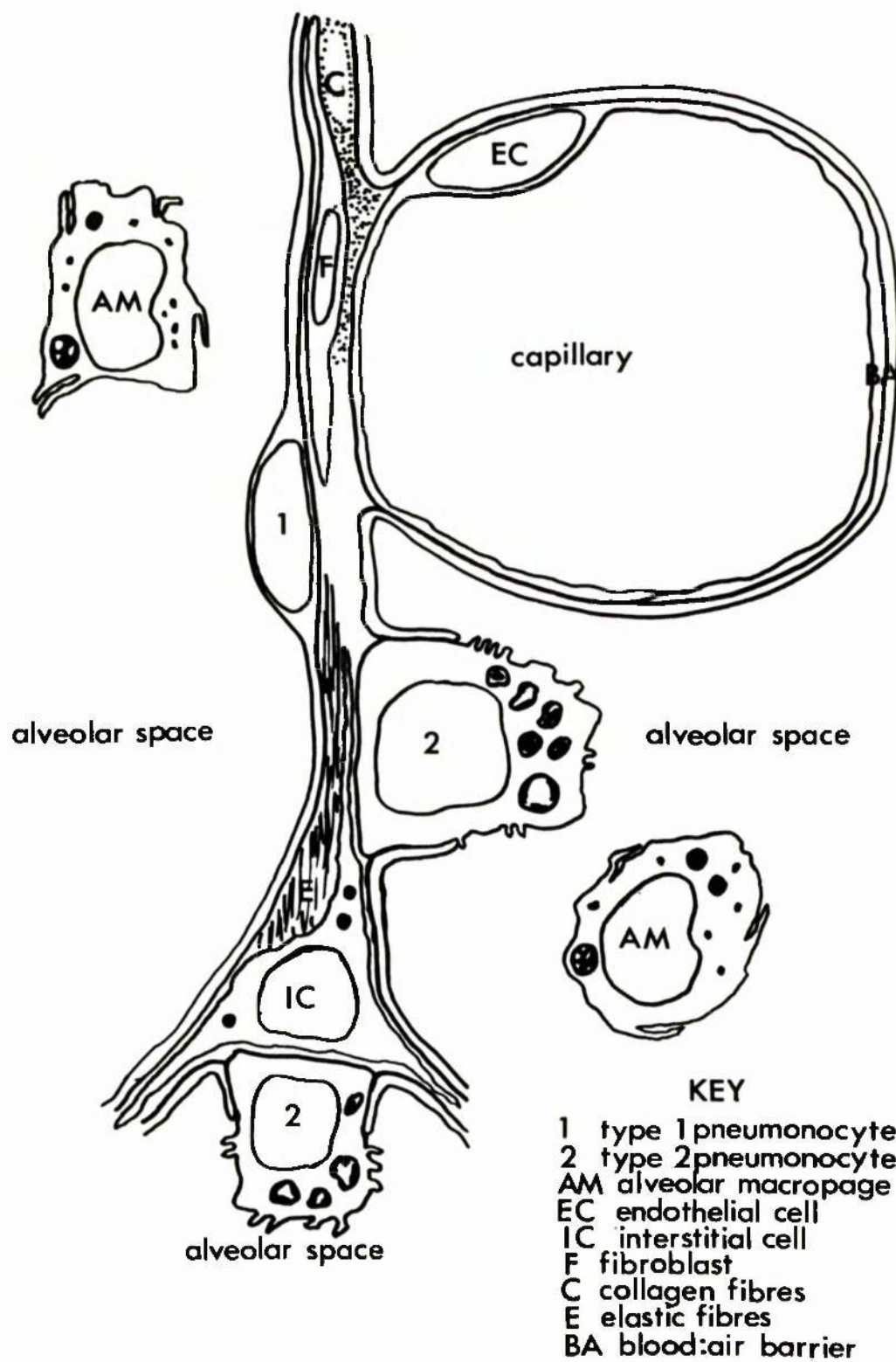
Brooks (1971a and b) has summarised the opposing view that surfactants are not essential in the normal lung and act to reduce surface tension only when fluid is present in the alveoli, e.g. after birth, in disease and in response to some toxic agents.

Bertalanffy (1964a and b) reviewed the structure of the alveolar wall, as did Omar (1964a). Their concepts of the structure of the alveolus have been rapidly overtaken by recent developments in electron microscopy and observations on alveolar cell relationships and dynamics. A diagram of the arrangement of the alveolar wall is provided below (Fig.108).

The nomenclature of cells of the alveolar wall is summarised in table (20).

PRESENT NAME OF CELL	PREVIOUS NAMES
<p>TYPE 1 PNEUMONOCYTE</p> <p>(Meyrick and Reid 1968)</p>	<p>Membranous pneumonocyte (Macklin 1954)</p> <p>Septal cell (Policard et al 1954)</p> <p>Type A (Yasudo 1958)</p> <p>Small alveolar (Policard et al 1959)</p> <p>Type 1 (Campiche 1960)</p> <p>Pulmonary surface (Bertalanffy 1965)</p>
<p>TYPE 2 PNEUMONOCYTE</p> <p>(Meyrick and Reid 1968)</p>	<p>Granular pneumonocyte (Macklin 1954)</p> <p>Alveolar cell (Policard et al 1954)</p> <p>Specific cell (Kisch 1955)</p> <p>Type B (Yasudo 1958)</p> <p>Large alveolar (Policard et al 1954)</p> <p>Type 2 (Campiche 1960)</p> <p>Alveolar (Bertalanffy 1965)</p>
<p>TYPE 3 PNEUMONOCYTE</p> <p>(Meyrick and Reid 1968)</p>	<p>-</p>
<p>ALVEOLAR MACROPHAGE</p> <p>(Karrer 1956)</p>	<p>Dust cell (von Ins 1876)</p> <p>Alveolar phagocyte (Briscoe 1908)</p>
<p>INTERSTITIAL CELLS</p> <p>(Bowden et al 1969)</p>	<p>Septal cell (Rhodin 1963)</p> <p>Intra-septal cell (Policard et al 1956)</p> <p>Alveolar (septal) cell (Curry et al 1969)</p>

Table (20). The nomenclature of cells of the alveolar wall.



fig(108). Diagrammatic representation of the structure of the alveolar wall

THE STRUCTURE OF THE BOVINE LUNG

Standard veterinary texts describe the gross anatomy of the bovine lung (Nickel, Schummer and Seiferle 1960; Sisson and Grossman 1962). The right lung is divided into apical, cardiac, intermediate and diaphragmatic lobes; the apical lobe is further divisible into a cranial and caudal part. Only apical, cardiac and diaphragmatic lobes, make up the left lung and there is no subdivision of the apical lobe. Stamp (1948) has charted the broncho-pulmonary segments of the bovine lung and the distribution of the airways. The right apical lobe is supplied by a bronchus which originates directly from the trachea about 10cm. cranial to the bifurcation and this 'eparterial bronchus' divides to supply the cranial and caudal divisions of the lobe, which each have four broncho-pulmonary segments. Bronchi from the two divisions of the trachea are given to the remainder of both lungs. The number of broncho-pulmonary segments in each lobe is as follows: right cardiac, 9; right diaphragmatic 18; intermediate 2; left apical 5; left cardiac 14; left diaphragmatic 15; the total number of broncho-pulmonary segments of both lungs is 71.

Latex injection techniques were employed by McLaughlan, Tyler and Canada (1961) to follow blood vessels and airways of the lungs of several species of mammal to their smaller ramifications. Three subgross lung types were distinguished: type 1 was represented by cattle, swine and sheep; type 2 by the dog, cat and monkey; and type 3 by the horse and man. Exceptional development of a secondary lobule structure and interlobular septa along with a thick pleura were singular features of type 1. Respiratory bronchioles were poorly developed, with only minimal alveolar budding taking place prior to junction with the alveolar duct. The most distal airway was the terminal bronchiole, which lead directly into an alveolar duct. Branches of the pulmonary artery and

vein and bronchial artery coursed with the bronchial tree to the distal terminal bronchioles. The bronchial artery supplied the hilar lymph nodes, pleura and bronchi and formed vasa vasorum with the pulmonary artery, and, to some extent, the pulmonary vein, before ramifying in the distal terminal bronchioles. Branches of the pulmonary artery were the main supply to the remainder of the terminal bronchioles, the alveolar ducts and the alveoli. A common capillary bed, beginning at the terminal bronchiole, mixed blood of pulmonary arterial and bronchial arterial origin, although a small number of bronchial-pulmonary arteriolar anastomoses were present at this level. Arterial blood from all levels drained via the pulmonary vein, with the exception of the first 2-3 divisions of the trachea, where the azygos system carried blood back to the heart (Liebow 1953).

Small pulmonary arteries and arterioles were noted to be muscular down to a diameter of about 20 microns and the muscularis was said to be thick and markedly contracted (Hecht 1959). Alexander and Jensen (1963) contradicted this claim and demonstrated that the muscular coat of pulmonary veins had led to their being misinterpreted as arteries. The pulmonary artery, down to branches with a diameter of approximately 20 microns, had a muscular media and this had no abrupt disruptions. Branches of the pulmonary vein, with diameters from 20-400 microns also possessed a well developed, muscular media. Wagenvoort and Wagenvoort (1969) found these muscular prominences of the pulmonary veins were absent in newborn calves but appeared soon after birth.

The blood vessels of the bovine lung appear to be innervated in an unusual way compared to other animals. Hebb (1969) used the methods of Lewis (1961) to trace cholinergic nerves in the lung, and a modified Falck fluorescent technique to detect adrenergic fibres (Falck 1965; Hebb, Mann and Perkins 1966). Large arteries of calf lung were found to have a sparse cholinergic innervation, with endings along the outer

border of the media, though nerves were present at the origins of arterial branches as small as 60- 70 microns in diameter. Cholinergic fibres were detected in bronchial muscle and in the wall of lobar branches of the pulmonary vein. Adrenergic innervation of the pulmonary artery was poor in comparison to other animals but on the other hand, a singular arrangement of fibres was present in the larger veins. The lobar, intra-pulmonary branches of the pulmonary vein had an evenly spaced supply of nerve fibres, interspersed with mast cells. Where the pulmonary vein emerged from the lung, there was an abundance of nerve fibres through the thickness of the wall and apparently traversing the media, but nearer again to the heart, the innervation was once more reduced. Hebb compared this to a sphincter muscle arrangement. Adrenergic fibres were also found supplying the bronchial muscle.

There have been few investigations of the fine structure of the respiratory tissues of cattle. A standard veterinary histology reference (Trautmann and Fiebiger 1952) described the structure of the conducting and respiratory portions of the mammalian lung, including that of the cow. At the time this book was published, it was not known whether an alveolar surface epithelium existed in mammals. Addison (1842), using the light microscope, mentioned the existence of flat cells, which may have been type 1 pneumonocytes, in the lungs of cattle and rabbits. Addison's findings began a controversy which lasted until Low and Daniels (1952) demonstrated a continuous alveolar epithelial lining in the rat.

Epling (1964a) confirmed that an epithelial lining, similar to that of other animals, was present in the ox. He examined the lungs of 20 mature slaughterhouse cattle by electron microscopy and found that a continuous epithelium of two cell types, resting on its own basement membrane, covered the alveolar surface. Capillaries lay in the space between two alveoli, along with occasional cells and connective tissue

elements. Endothelial cells of the alveolar capillaries lay on a basement membrane, which in many cases was fused to that of the surface epithelium to form a minimal diffusion barrier. "Free cells" were present in the alveolar lumen. One type of epithelial cell was flattened, with attenuated cytoplasm; the other was more cuboidal and projected into the lumen; both cells were found to have microvilli on their free borders. Adjacent epithelial cells were not joined by desmosomes but were separated by a space 200 Angstroms wide. The cell which projected into the lumen had many vacuoles, some of which contained dense, osmiophilic, lamellar inclusions. Free cells present in the alveolar lumen contained osmiophilic, lamellar bodies of similar appearance. The capillary endothelial cells were not fenestrated and were separated at their junctions by a 200 Angstroms wide gap; capillaries were classified as type A-1- α using the scheme proposed by Bennett et al (1959). Cells present in the interstitium were classified predominantly as fibroblasts, with occasional lymphocytes, macrophages, mast cells and plasma cells. The way by which these cells were distinguished ultrastructurally was not described. The only cell illustrated in the alveolar interstitium was not identified as any of these cell types but was referred to as a connective tissue cell.

Epling (1964b) recorded many lattice and lamellar bodies in the alveolar spaces of 5 out of 20 normal bovine lungs examined. These bodies were composed of membranes 60-80 Angstroms thick, separated by spaces 100-700 Angstroms wide. The function of these was not determined, but a relationship to the alveolar surfactant was postulated. Epling (1966) observed cells resembling pericytes in the bovine lung and illustrated processes of these cells in contact with basement membrane of capillary endothelial cells. The factors which defined the pericyte were not stated and the distinctions between these cells and other cells in the interalveolar septum were not drawn.

The electron microscopic descriptions of the structure of the bovine lung have been superseded by recent developments and studies in the lung cytology of other species. Characteristic features of the lung cells and alveolar morphology were incompletely defined, and it was obvious that baselines would need to be drawn before beginning ultrastructural studies in bovine respiratory disease. Some of the cell types in the normal bovine lung have been identified in figure (109).

RESULTS: THE NORMAL BOVINE LUNG

Alveolar epithelium began abruptly where the cytoplasm of a type 1 pneumonocyte abutted directly against the cytoplasm of a cuboidal bronchiolar epithelial cell (Fig. 111).

Two morphological types of cell were identified in the alveolar epithelium and these were classified as the type 1 and type 2 pneumonocytes. Free cells, alveolar macrophages, were common in the alveolar spaces. Capillaries, pericytes, interstitial and connective tissue cells and fibres were observed in the alveolar walls.

Type 1 pneumonocyte

The type 1 pneumonocyte was squamous and its thicker perinuclear cytoplasm attenuated rapidly to form thin lateral sheets which covered large areas of the interalveolar septum (Figs. 112, 113). The cell was thickest in the nuclear region and the Golgi apparatus and occasional mitochondria were found in this site; the nucleus was elongated or oval with one or more nucleolus in many cases (Figs. 112, 114). Organelles were infrequently seen in the cytoplasm peripherally, perhaps because the cell covered a large area and only a small portion could be examined at one time. A moderate number of profiles of smooth surfaced endoplasmic reticulum (SER) and, infrequently, rough surfaced endoplasmic reticulum, (RER) were scattered through the cytoplasm, in which small vesicles, occasional small dense inclusions and free ribosomes were also found. A large number of pinocytotic vesicles could be found both at the luminal and basal borders of the cell (Fig. 115). The cell outline was generally smooth, but occasional short, stumpy processes or microvilli were seen singly on the free border. The cell rested on a basement membrane which was continuous with that of other epithelial cells (Figs. 112, 115).

The nucleus of the cell could be observed with the light microscope, but could not be distinguished with confidence from that of the capillary endothelial cell (Fig. 113). The cytoplasmic extensions were not differentially stained and were at or beyond the limit of resolution of the light microscope. These extremely fine cytoplasmic plates covered the alveolar capillaries, which bulged into the lumen, and with the basement membranes and capillary lining cells made up the blood: air barrier (Figs. 113, 116). The type 1 pneumonocytes joined to each other, and to type 2 pneumonocytes, by tight cell junctions of the zonula occludens type (Fig. 115).

Type 2 pneumonocyte

This cell was roughly cuboidal in shape and was often found projecting into the lumen at the angle formed by the junction of adjacent alveolar septa (Fig. 112). Cells were found singly on the wall and often appeared to overlies interstitial cells within the wall, from which they were separated by a basement membrane (Fig. 117). Occasional cells were mushroom shaped and attached to the septum by a short, stumpy stalk, which was overhung laterally by extensions of cytoplasm. Accordingly, sections were found in which portions of typical type 2 cell cytoplasm might be found some distance away from the epithelium. These 'free' portions probably represented sagittal sections through an overhanging edge.

The spherical nucleus often contained one or more nucleoli and was found towards the base of the cell. The free surface of the cell (Fig. 117) was thrown into a variable number of irregular, short microvilli, with the exception of the basal parts, which were covered by overlapping cytoplasmic extremities of type 1 cells, forming tight cell junctions (Figs. 112, 118). Organelles and inclusions were common in the cytoplasm;

mitochondria were abundant, SSER was well developed and its cisternae were often dilated and prominent. The lamellae and vesicles of the Golgi apparatus were regularly found at the base of the cell in a perinuclear position, but in some instances were also apparent at the apex, away from the nucleus, since in this cell the organelle was well developed. Small multivesicular bodies could be distinguished in close association with vesicles of the Golgi zone. RSER was present to a lesser degree than SSER, though free ribosomes were found in large numbers, especially in the apical cytoplasm. One characteristic feature of type 2 cells was the presence of irregularly sized, round or ovoid, inclusion bodies, which exhibited a variable degree of osmiophilia (Figs. 119, 120). The inclusion bodies varied in size, the larger ones being found at the apex and the smaller at the base, near the perinuclear Golgi lamellae. These inclusions, which were membrane bound (Fig. 121), were frequently empty or contained different amounts of electron dense material, which was homogenous or arranged in complex scrolls (Figs. 119, 122). When the inclusions were whorled, they often consisted of an outer, densely osmiophilic rim about a central lamellar core of parallel, thick electron dense bands separated by an electron lucent space. The structure of the contents differed in inclusions of the same cell (Fig. 119). Smaller inclusions, near the Golgi, had homogenous contents in most cases (Figs. 120, 122). Type 2 pneumonocytes could be distinguished with the light microscope. However, the alveolar macrophage was very similar in appearance and in many instances it was difficult to differentiate the two.

Alveolar Macrophage

Alveolar macrophages were free cells found in varying numbers in the lumen of the alveolus. They occasionally rested on epithelial cells or remained unattached, but did not form cell to cell junctions. Most macrophages had an irregular outline with small pseudopod processes of differing size (Fig.123). The nucleus was usually eccentric and often indented, forming a bean shape; a single prominent nucleolus could sometimes be discerned. Very many mitochondria were present in the cytoplasm and a discrete Golgi zone was apparent close to the nucleus. RSER was sparse, but there were many free ribosomes, small vacuoles and vesicles in the cytoplasm. Membrane bound phagosomes of uneven size with pleomorphic internal contents were found in moderate numbers (Fig.123). Occasional single phagosomes contained myelin-like, lamellar structures similar to those of the type 2 cell inclusion (Fig.123). Phagocytosed cells, mainly polymorphonuclear leucocytes and lymphocytes were observed from time to time. The plasma membrane of the cell was often infolded in many places, forming long curving lines in electron micrographs. A feature of the macrophage was the presence of small, round, lysosomes, which were membrane bound and had homogenous, electron dense contents (Fig. 124).

Capillary endothelial cell

This cell was thickest in the nuclear region and its cytoplasmic processes attenuated laterally over a considerable distance (Fig.112). The nucleus was large and occasionally crenated; a Golgi zone, mitochondria and single, small, electron dense inclusions were found perinuclearly (Fig. 125). The peripheral cytoplasm contained very large numbers of vesicles and vacuoles and small profiles of RSER (Fig.125). Pinocytotic vesicles in large numbers were found at both surfaces of the cell, opening from the capillary lumen and the basement membrane (Fig.116).

The endothelial cell cytoplasm was thrown into short processes, which projected into the capillary lumen in some preparations.

Endothelial cells rested on their own basement membranes; in the attenuated, peripheral areas of the cells, the basement membranes of endothelial cells and type 1 pneumocytes were fused, without intervening structures (Fig. 116). The endothelial cells were joined at their overlapping cell edges by junctional complexes and in some cases extensive interdigitation was obvious (Fig. 125).

Pericyte

Pericytes were found closely applied to the capillary endothelial cells and were surrounded by basement membrane continuous with that of the endothelial cell on all sides (Fig. 126). The cells were slender and strap-like, running around the periphery of the capillary. Pericytes were relatively featureless; the nucleus was small and round, and the granular cytoplasm devoid of any organelles other than occasional mitochondria, the Golgi apparatus, and a few fine filaments (Fig. 127). Small processes of the pericytes interdigitated with endothelial cells, though they were always separated by basement membrane.

Interstitial cells

The interstitial cells lay between the basement membranes of the alveolar epithelial cells and the capillary endothelium (Fig. 128). They were found, therefore, in the connective tissues which formed the interstitial sheet of the alveolar wall (Fig. 114). Two morphological types of cell were observed.

The first was fusiform in shape, in many sections, with a long, slender nucleus, but was also found with the cytoplasm extending in several directions in a stellate fashion beneath the epithelial basement membrane, and in this case the nucleus was round (Fig. 128). The

perinuclear cytoplasm contained the organelles : a large Golgi zone, numerous mitochondria, profiles of RSER, a moderate number of free ribosomes and many vesicles and cisternae of SSER. Membrane bound lysosomes (Fig. 129) with densely osmiophilic contents were present along with occasional single phagosomes containing pleomorphic material. Some small tips of stellate processes appeared to interdigitate with endothelial cells, like the pericyte, though remaining outwith the basement membrane. These processes of the cell often contained only granular cytoplasm. (Fig.115).

Numerous, large, membrane bound vesicles and vacuoles filled the cytoplasm of the second variety of interstitial cell (Figs.120,130). Most of these vesicles were empty, but a few contained granular material. Mitochondria were observed in the perinuclear region but there were few other organelles. The nucleus was roughly oval and a few short processes projected from the cell surface. Lysosomes and lipid vacuoles were not apparent.

Other cells of the alveolar septum

Plasma cells and lymphocytes were uncommon in alveolar walls of normal subjects, except in the peribronchiolar region. Mast cells were more numerous, with the light microscope, but all these cells were encountered relatively infrequently in electron microscopical preparations of the same material and were found in the interstitial space.

Plasma cells

Plasma cells occurred singly or in small clusters in the thicker parts of alveolar septa adjacent to some bronchioles. The cells had a large round nucleus often with a single nucleolus, and a large Golgi zone situated in a juxta-nuclear position. The remainder of the cell was occupied almost entirely by tightly packed, narrow arrays of cisternae of RSER. Sometimes the cisternae of RSER were very much dilated and

contained an homogenous material, which was slightly electron dense.

Mitochondria were interspersed between the stacks of RSER.

Lymphocytes

Occasional small lymphocytes were present in the capillary lumen or in the interstitial space. The nucleus was round and filled much of the cell; the peripheral rim of cytoplasm contained one or two mitochondria and small clusters of free ribosomes.

Mast cells

Mast cells were observed around bronchioles and bronchi and in their smooth muscle; in the intericubular and pleural connective tissue and, to a lesser extent, in the alveolar interstitium in sections stained with toluidine blue, pH 4.5, or astra/blue safranin. Cells were infrequently found in E.M. preparations of the alveolar wall. Mast cells were roughly oval in outline and the round nucleus was often situated to one edge of the cell. The cytoplasm contained many round, membrane bound granules, with a homogenous electron dense content. A well developed Golgi complex was located in a paranuclear position. Mitochondria were present between the granules in the cytoplasm.

Neutrophil

Neutrophils were frequently observed in the capillary lumen and were distinguished by their lobed nuclei and abundant, variably shaped, irregularly sized, lysosomal inclusions.

Fibroblast

The fibroblast was an elongated cell present in the interstitial spaces, especially in thicker parts such as the alveolar duct where it lay amidst bundles of collagen and elastic fibres. A round or oval nucleus

with an occasional nucleolus was generally found about the middle of the cell; the cytoplasm was drawn out beneath the epithelial cells in finger-like processes. The main feature of the cell, abundant RSER, was present in the form of unequally dilated cisternae in the peripheral cytoplasm. The cisternae contained material of moderate electron density.

Basement membranes

The epithelial and endothelial cells rested on continuous basement membranes, which were separate and distinct around cellular or acellular interstitial components, but which were fused over much of the surface of the lung capillaries, with minimal interstitial substance, to form part of the blood:air barrier. In situations where the membranes were separate, they could be seen as a narrow lucid band (lamina lucida) adjacent to the cell, with a more electron dense granular layer (lamina densa) immediately and beneath. The deep border of the lamina densa blended with the subjacent tissue space to form a moderate electron dense zone (zona diffusa) (Fig. 115). Basement membrane surrounded the pericyte of the alveolar capillary on all sides (Fig. 127).

Interstitial connective tissue

The alveolar epithelium covered a central connective tissue core, which contained several types of cell described above. Bundles of microfibrils, with the periodicity of collagen, and thicker fibres and bundles of elastin were found in the interstitial space, especially near alveolar ducts (Figs. 131, 132). In this position, smooth muscle spindles might also be encountered. Amorphous ground substance was present between microfibril bundles, cells and basement membranes. No nerves or lymphatic vessels were encountered in the alveolar septa examined. The capillaries of the alveolar wall were generally discovered bulging into the lumen from either side of a central connective tissue core, through which the capillaries freely anastomosed (Fig. 113).

Surfactant

An acellular lining layer was not seen in this study, but occasional myelin like figures and lattice configurations were identified in the alveolar lumen (Fig. 144). Some preparations fixed with 2% glutaraldehyde exhibited an electron dense granular lining layer which formed a concave lining to the alveolus over part of the surface. Such observations were infrequent.

Junctional complexes

Adjacent type 1 and type 2 pneumonocytes were joined by tight junctional complexes of zonula occludens type. The lateral plasmalemmata of adjacent cells came together and fused, at the luminal surface forming the zonula occludens. Nearer again to the basement membrane was the zonula adhaerens, where the membranes were closely applied but separated by a small space filled with moderately electron dense material. Beneath the zonula adhaerens was the desmosome, or macula adhaerens, from which fine filaments radiated into the cytoplasm (Fig. 118a & b).

DISCUSSION

The morphology of the alveolar wall of the normal cow was basically similar to that described in other mammals (Curry et al 1969; Meyrick and Reid 1970) and previously in cattle by Epling (1964a).

A continuous cellular layer, composed of type 1 and type 2 pneumonocytes, covered the interalveolar septum; this was in agreement with the results of Epling (1964a). Type 3 pneumonocytes, described by Meyrick and Reid (1968) in the rat, were not seen. Low and Sampaio (1957) claimed that terminal bronchiolar epithelial cells became gradually flattened at the origin of the alveolar duct. Such transitional forms were not found in this study: the type 1 pneumonocytes were immediately adjacent to the distal, cuboidal, bronchiolar epithelial cell.

Type 1 pneumonocytes were joined to each other and to type 2 pneumonocytes by tight junctional complexes. Epling (1964a) claimed that a 200 Angstrom wide gap separated adjacent epithelial cells. He fixed the lung tissues in 40% osmic acid and the cell separation may have resulted from this choice of fixative. Such cell separation was not found in either the epithelium or the endothelium of well fixed specimens in this study.

The inclusions of the type 2 pneumonocyte did not appear to be as electron dense and obviously lamellar as those of other species (Curry et al 1969; Meyrick and Reid 1970). This may have represented a difference in the fixation properties of the inclusion contents between the species. Dermer (1969) has presented chemical reasons for the failure of the material in the inclusions to be fixed by the conventional fixatives glutaraldehyde or osmic acid. The contents include dipalmitoyl lecithin, a surfactant, which is a saturated phospholipid unfixed by these two methods.

If this is so, the lamellar material retained in the inclusions must be of different composition from the surfactant. Empty vacuoles may have been empty initially or have contained saturated phospholipids removed during processing. Lattice figures found occasionally in the lumen possibly represented extruded inclusions or their contents or residues of the surfactant.

The basement membranes of the epithelium and endothelium were comparable to those described by Low (1961); the alveolar epithelial basement membrane was continuous with that of the terminal bronchiole.

Bennett et al (1959) proposed a scheme for designating capillary types using a 3 figure notation:-

- capillary type A - with a continuous basement membrane
- " type B - without a continuous basement membrane
- " type 1 - without fenestrations or pores
- " type 2 - with intracellular fenestrations or perforations
- " type α - without a complete pericapillary cellular investment
- " type β - with a complete pericapillary cellular investment.

The capillaries of the bovine lung had a continuous basement membrane, were without fenestrations and without a complete pericapillary cellular investment; they were classified as A-1- α . Capillaries bulged into the alveolar spaces and anastomoses between capillary networks of adjacent alveoli frequently traversed the septum. Capillaries also lay on either side of a central connective tissue sheet in a manner very like that reported in the hamster lung (Ryan et al 1969); an arrangement which provided for optimal diffusion area and a minimal blood : air barrier.

Pericytes were observed infrequently. Epling (1966) recorded these cells in 20% of capillary sections from bovine lungs. He did not define the characteristics of these cells, but cited Rouget (1873), who described such cells in amphibia. Ham (1969) stated that the pericyte was intimately associated with the walls of capillaries and was

surrounded on all sides by basement membrane. Epling (1966) did not report interstitial cells in the lung. An investing layer of basement membrane could not be clearly discerned in the illustrations of pericytes he provided; in my view, the evidence that pericytes were so frequent in the lung was not convincing. Interstitial cells and their processes and the interdigitations of endothelial cells had probably been confused with pericytes in some cases where the nucleus of the pericyte was not visible in the electron micrograph. Such a high incidence of pericytes has not been suggested by this study, although the cytoplasmic extensions of interstitial cells were found very frequently.

The bovine alveolar macrophage was similar to that of the mouse (Karrer 1956, Curry et al 1969). Pinkett et al (1966) demonstrated that many alveolar macrophages were derived from blood monocytes. Bowden et al (1969) have confirmed and expanded this work and have indicated that some of the interstitial cells represent an intermediate stage, possibly of multiplication and maturation, in macrophage development. It was interesting that many of the interstitial cells of the cow resembled alveolar macrophages, although the cytoplasmic organelles were not so numerous in the interstitial cells nor did they contain as many lysosomes as the free alveolar macrophages. Some interstitial cells could act as fixed macrophages, phagocytosing particles such as silicon after they penetrated the alveolar wall. Two morphological forms of interstitial cells were found, one with electron dense lysosomes, the other without. The lysosome containing cell was clearly reticulo-endothelial in appearance and, probably, function. The other cell appeared to be a degenerate cell, of unknown origin and function, and did not contain the lipid vacuoles described in an otherwise similar cell of the mouse (Curry et al 1969).

Epling (1964a) suggested that the capillaries of the bovine alveolus were few in number, compared to other species, and that very little elastin was present in the alveolar septum. He provided no facts to support this view and none have been offered since. The results of this study do not support this claim.

CYTOLOGY OF THE ALVEOLAR WALL IN FOG FEVER

INTRODUCTION

A continuous layer of cuboidal cells was found to line many alveoli in the lungs of animals with fog fever (Fig.110); this lesion was the most significant finding in the lungs of many animals slaughtered up to 7 days after the onset of clinical signs. Mackenzie (1966) has also described this cell proliferation in fog fever and implied that the alveolar epithelial cells were the source. A similar cell layer in alveoli was noted in parasitic bronchitis (Jarrett, MacIntyre and Urquhart 1954) and it was suggested that the multiplying cells might be derived from the epithelium of respiratory bronchioles or the alveoli. The histogenesis of the cells involved was not known and this study was designed to identify the proliferating cells by histochemical and ultrastructural methods.

HISTOCHEMISTRY

The proliferating cells could have been derived from the cells lining the bronchioles; the type 1 or type 2 pneumonocytes; the alveolar macrophage or its precursors.

Meyrick and Reid (1970) reviewed the histochemical properties of alveolar macrophages and type 2 pneumonocytes in the normal lung: the macrophages stained strongly with methods to demonstrate acid phosphatase, the type 2 cells stained weakly; alveolar macrophages did not contain diastase resistant PAS positive material, but type 2 pneumonocytes were found to react with this stain. An attempt was made to identify the proliferating cells in fog fever on the basis of their acid phosphatase content and PAS staining reaction.

Barka and Anderson (1962) compared the Gomori, AS-TR phosphate and α -Naphthyl phosphate methods for the demonstration of acid phosphatases in mammalian tissues; they found the AS-TR phosphate technique was most satisfactory. In this investigation, the AS-TR phosphate method of demonstrating acid phosphatases was used, as well as the P.A.S. stain before and after diastase, to identify cells in the normal bovine lung and the alveolar epithelium in fog fever.

MATERIALS AND METHODS

Tissues

Portions of lung were taken from six normal calves and six animals affected by fog fever at postmortem. The tissue from cases of fog fever was selected from parts of the lung thought to have alveolar epithelial hyperplasia on gross examination.

Small blocks of tissues for histochemical studies were rapidly frozen on dry ice ($-20^{\circ}\text{C}.$) then stored at $-20^{\circ}\text{C}.$ until used.

Tissues were also fixed in corrosive formol and these were processed by the means described in the general materials and methods section.

Stains

Cryostat sections of the selected tissues were fixed in formol calcium for 60 seconds and then stained by H & E and the Naphthol AS-TR phosphate method. No additive was used on the cryostat slides. Corrosive formol fixed sections were stained with P.A.S. and P.A.S. after diastase.

Staining methods1) The Naphthol AS-TR Phosphate-Hexazonium Pararosanilin method

(Barka & Anderson 1962).

Stock solutions were prepared as follows:

a) Pararosanilin solution

1gm Pararosanilin hydrochloride (SIGMA) was dissolved in 20ml distilled water and 5ml concentrated HCL using gentle heat. The solution was filtered after cooling and stored at room temperature.

b) Sodium nitrite

A 4% solution in distilled water was prepared weekly and stored at 4°C.

Hexazonium pararosanilin solution was prepared by mixing 0.8ml of each of solutions a & b in a test tube.

c) Naphthol AS-TR Phosphate

100mgm naphthol AS-TR phosphate (SIGMA) was dissolved in 10ml N,N-dimethyl formamide (SIGMA) and stored at 4°C.

d) Michaelis veronal acetate buffer

9.714gm sodium acetate $3 \cdot H_2O$ and 14.714gm sodium barbiturate were dissolved in carbon-dioxide free distilled water to a final volume of 500ml.

e) Methyl green counterstain

1% methyl green was prepared in 0.1 M phosphate-citric buffer, pH 4.0. The buffer was prepared from 5ml of solution d with 11ml 0.1 M HCL and 9ml distilled water.

f) Haemalum counterstain was Mayer's haemalum.Incubation method

Formol calcium fixed cryostat sections were incubated at 37°C. for 90 minutes in a medium of Naphthol AS-TR Phosphate and Hexazonium pararosanilin. The medium was prepared by adding 5ml Michaelis veronal acetate buffer to 12ml distilled water and 1ml Naphthol AS-TR phosphate stock solution; 1.6ml hexazonium pararosanilin solution was added and the final pH adjusted to 5.0 with INNaOH. After incubation, the sections were rinsed in distilled water, counterstained with methyl green for 2-3 minutes or haemalum for 5 minutes, rinsed again (and differentiated in S.T.W.S.* in the case of haemalum) then dehydrated quickly in alcohol, cleared in xylol and mounted in D.P.X.**

2) Other Stains

P.A.S. and P.A.S. after diastase was used routinely on corrosive formol fixed sections (Pearse 1968). Cryostat sections were stained by H & E for orientation.

*S.T.W.S. - Scott's tap water substitute.

** D.P.X. - B.D.H.

RESULTS

In the normal lung, cells found free in the alveolar lumen were classified as alveolar macrophages if the nucleus was indented or bean shaped and the fairly abundant eosinophilic cytoplasm contained small phagosomes or was finely vacuolated. Cuboidal cells with vacuolated apical cytoplasm were identified as type 2 pneumonocytes when they were present on the alveolar wall.

The alveolar spaces in some cases of fog fever contained many large mononuclear cells; some of these were obviously macrophages by the criteria above and others could not be positively identified in H & E stained sections. The degree of alveolar epithelial hyperplasia in the sections examined varied from 1+ to 3+ using the grading system defined previously. Mononuclear cells could be distinguished in the alveolar septa where it was thickened by oedema; these cells were classified as interstitial cells.

Results of the staining procedures in the normal lung and the lungs of cases of fog fever are summarised in tables (21) and (22). Type 1 pneumonocytes were not distinguished.

Normal lung

AS-TR phosphate staining of the normal lung resulted in finely granular, bright red colouration of the cytoplasm of alveolar macrophages, without nuclear staining. The apical cytoplasm of type 2 pneumonocytes was light brown-orange in colour. A few interstitial cells were identified and their cytoplasm was bright red. Background tissues were light yellow (Figs.133,134,135).

A few P.A.S. positive, diastase resistant, cytoplasmic granules were present in the apical cytoplasm of some type 2 pneumonocytes

These inclusions were not found in alveolar macrophages or interstitial cells.

Fog fever

Acid phosphatase staining of the lungs of fog fever cases (Figs. 136, 137) revealed that the cytoplasm of many of the cells in the lumen was coloured bright red with AS-TR phosphate. Other cells in the lumen were not stained so intensely, and their cytoplasm was light brown-orange in colour. The cells forming the cuboidal alveolar epithelium either did not stain or stained very lightly yellowish-brown with AS-TR phosphate; their nuclei did not stain. Simuous or round cells, in which there was intense, red staining of the cytoplasm, were frequently seen in the alveolar septa. Simuous cells were apparently in the alveolar interstitial tissue, and the round cells in blood capillaries (as Fig. 135).

P.A.S. staining of the lungs of fog fever cases revealed the presence of P.A.S. positive, diastase resistant, hyaline membranes or deposits in alveolar spaces in almost every instance. Large, discrete, diastase resistant, P.A.S. positive granules were found in almost all the free alveolar cells, most of which were certainly macrophages and some of which had also ingested R.B.C's or polymorphs. A little P.A.S. positive diastase resistant material was also found, in smaller granules, in the apical cytoplasm of a few of the cells lining the alveoli. P.A.S. positive material was not seen in the interstitial cells.

Electron microscopy

In every case of fog fever, the alveolar epithelium was found to be composed of cells resembling the type 2 pneumonocytes.

The hyperplastic cuboidal cells were found to have many short microvilli over their free surfaces, especially laterally and to be joined to each other by complex interdigitations and tight junctional complexes of the zonula occludens type (Fig.138,139). Cells were mostly cuboidal in shape and rested on a basement membrane, which was either fused with that of the underlying capillary endothelial cells or covered interstitial tissue (Fig.138). The alveolar epithelium was almost always a single cell layer, but, occasionally, a portion of the cytoplasm of a type 1 pneumonocyte which lay on its own basement membrane was identified beneath the hyperplastic epithelium. Alternatively, a double layer of type 2 pneumonocytes was infrequently seen, the lower cell rested on a basement membrane over the alveolar septum, the luminal cell was attached by cell junctions to the lower.

The basal nucleus of the cuboidal cells was round, hyperchromatic and often contained an obvious nucleolus. Cytoplasmic organelles were exceedingly numerous: the Golgi apparatus was particularly well developed and the stacked lamellae and vesicles of this organelle were apparent in the basal and apical portions of the cell (Fig.140). Small membrane bound vesicles, which contained variably electron dense, homogenous bodies were often found in the lower parts of the cell; these small, multivesicular bodies were often associated with lamellae of the Golgi apparatus (Fig.141). A singular feature of all cells was the presence of a variable number of unevenly sized, membrane bound, irregularly lamellated or whorled, unevenly electron-dense, inclusion bodies in the cytoplasm, usually of the apical part of the cell (Figs. 141,142). The smaller of these electron-dense inclusions were lamellated but otherwise similar to the multivesicular bodies. Many segments of smooth surfaced endoplasmic

reticulum, a large number of glycogen granules, free ribosomes and mitochondria were apparent in the cells.

An unusual observation in the alveolar epithelium of one animal was the presence of an apparently membrane bound collection of vesicles in the apical cytoplasm of type 2 pneumonocytes (Fig. 143). The nature of these vesicles was obscure but there was a superficial resemblance to dilated R.S.E.R. However, R.S.E.R. is composed of an inner smooth surfaced membrane with small granules on the outer surface, adjacent to the cytoplasmic matrix, whereas the vesicles in the pneumonocytes had, in most cases, a smooth outer membrane with granules on the inner surface, away from the cytoplasmic matrix.

Similar cuboidal cells to those found in the epithelium were seen in the alveolar spaces; these were apparently desquamated type 2 pneumonocytes. Many alveolar macrophages were found free in the lumen also; these cells were distinguished by their very irregular outline, since the cytoplasm was thrown into long cytoplasmic extensions (Fig. 144). The bean-shaped nucleus was generally hyperchromatic and phagosomes, often containing polymorphonuclear leucocytes or eosinophils were present in the cytoplasm. Many bundles of fine filaments were present in the perinuclear cytoplasm and occasional folds of the plasma membrane were discovered. Discrete, membrane bound, round, homogenous, electron-dense lysosomes were usually present in these cells also.

Interstitial cells were very common beneath the type 2 pneumonocytes and their basement membrane (Figs. 138, 139) and many of the interstitial cells contained lysosomes (Figs. 138, 139).

Fibrillar material (Fig. 145) resembling fibrin, was often found in the alveolar spaces, where it was mixed with oedema fluid and neutrophils.

STAIN	ALVEOLAR MACROPHAGE	INTERSTITIAL CELL	TYPE 2 PNEUMONOCYTE
AS-TR PHOSPHATE	+++	+++	+
P.A.S. after diastase	-	-	+or-

Staining reactions graded on arbitrary scale

- absent, + slight, ++ moderate, +++ marked.

Table (21) Staining reactions of alveolar macrophages, type 2
pneumonocytes and interstitial cells of the
normal bovine lung.

STAIN	LARGE MONONUCLEAR CELLS IN ALVEOLAR SPACES	ALVEOLAR EPITHELIUM	CELLS IN ALVEOLAR WALL
AS-TR PHOSPHATE	+++ or +	+	+++
P.A.S. after diastase	++ or -	+or-	-

Staining reactions graded on arbitrary scale

- absent, + slight, ++ moderate, +++ marked.

Table (22) Fog fever: staining reactions of large mononuclear cells in alveolar spaces; alveolar epithelium and cells in the alveolar wall.

DISCUSSION

The staining reaction with AS-TR phosphate in the normal bovine lung indicated that the alveolar macrophages contained acid phosphatase in large amounts. A lighter degree of staining of type 2 pneumonocytes was observed and this has been noted in these cells in other species (Sorokin 1967). Type 2 pneumonocytes have not been found to be actively phagocytic and the phosphatase enzyme content was attributed by Corrin (1970) to enzymes involved in lipid metabolism in the lamellar inclusions; these enzymes were believed to be involved in surfactant production.

The incubation time with AS-TR phosphate was longer than that normally necessary for demonstration of acid phosphatase activity (Barka and Anderson 1962) and this was attributed to loss of enzyme activity whilst the material was stored at -20°C .

Sorokin (1967) found P.A.S. positive, diastase resistant material in type 2 pneumonocytes of a variety of animal species; alveolar macrophages did not contain this substance. Some bovine type 2 pneumonocytes also possessed small cytoplasmic granules with similar staining properties; the exact nature of this substance in bovine and in other tissues is not known (Sorokin 1967).

The histochemical studies described here indicate that the bovine type 2 pneumonocyte and alveolar macrophage stain in a similar manner to those of other animals (Sorokin 1967).

Histochemical investigation of the alveolar epithelial cells in cases of fog fever indicated that these cells stained lightly with the acid phosphatase technique and were not, therefore, alveolar macrophages. Some of the cells in the alveolar spaces did react strongly with the acid phosphatase medium and were classed as alveolar macrophages.

The lightly coloured cells in the alveolar spaces and the cells in the alveolar epithelium were stained similarly to type 2 pneumonocytes.

P.A.S. positive material which was diastase resistant was found in some cells in the alveolar epithelium and in many of the free cells. Since there were hyaline membranes in many alveoli, it was probable that they were the source of the diastase resistant, P.A.S. positive inclusions in the obviously phagocytic cells in the lumen. Alveolar macrophages were frequently seen in hyaline membranes and deposits. Although the P.A.S. positive material appeared more abundant in alveolar macrophages, the P.A.S. technique was not of any value in distinguishing the cell type in these circumstances.

The results of the ultrastructural investigation have demonstrated that the hyperplastic alveolar epithelium in cases of fog fever was composed of type 2 pneumonocytes and that the free cells in the alveolar spaces were a mixture of type 2 pneumonocytes and alveolar macrophages.

The position of the proliferating cells on a basement membrane and the tight junctional complexes between adjacent cells were consistent with an epithelial origin: in addition, the cuboidal shape, surface microvilli and lamellated inclusion bodies characterised the type 2 pneumonocyte of bovine and ^{of} mammalian lung (Meyrick and Reid 1970).

Type 2 pneumonocytes in fog fever were hyperchromatic and contained more organelles, glycogen and dense or lamellated inclusions than those in the normal lung. The mitotic figures, which were frequently seen with the light microscope, indicated that the type 2 pneumonocytes were proliferating rapidly on the wall; there was no light microscopic or ultrastructural evidence to suggest that type 1 pneumonocytes formed a significant proportion of the cuboidal, lining cells.

A number of the free, large mononuclear cells in the alveolar lumen were found to be type 2 pneumonocytes histochemically and ultrastructurally. Alveolar macrophages were observed to be similar in size and shape to type 2 pneumonocytes with the light microscope. Ultrastructurally, however, they lacked the distinguishing characters of the type 2 pneumonocyte mentioned above and possessed other typical features, including intra-cytoplasmic phagosomes and lysosomes and long, superficial, cytoplasmic processes. Alveolar macrophages in cases of fog fever contained more obvious cytoplasmic filaments, which were probably involved in cell movement, and had a more irregular outline than macrophages of the normal lung.

One interesting observation was the identification, in the alveolar walls, of cells containing acid phosphatase - occasionally in the normal lung but more frequently in cases of fog fever. Bowden et al (1969) have demonstrated that a proportion of alveolar macrophages were derived from interstitial cells. Large numbers of alveolar macrophages could be seen in the alveolar spaces of animals affected by fog fever. This increase in number could have been reflected by more numerous interstitial cells supplemented by migrating blood monocytes from the capillaries. It is probable that only the interstitial cells that contained lysosomes stained for acid phosphatases: it is not known whether all interstitial cells contain these enzymes.

Proliferation of cells resulting in a continuous cuboidal alveolar lining layer has been referred to as "alveolar epithelialisation" (Jubb and Kennedy 1963 and 1970 and others). This term was adopted at a time when the existence of a continuous alveolar lining of epithelial cells was in dispute, and since it is now accepted that there is such an epithelium, the term is not as useful.

Alveolar epithelial hyperplasia is a more accurate description of the pathological process and this term has been used as a replacement for 'alveolar epithelialisation', particularly where the cell type has been identified.

Alveolar epithelial hyperplasia occurs in several diseases of man and animals and the proliferating cell type has been identified as the type 2 pneumonocyte in Jaagsiekte of sheep (Wandera and Krauss 1971; Perk et al 1971), which is thought to be a virus induced neoplasm; desquamative interstitial pneumonia and diffuse fibrosing alveolitis of man (Brewer et al 1969; Shortland et al 1969, Leroy 1969; Gould et al 1971; Farr et al 1970); paraquat (Toner et al 1970; Butler 1970) or Crotalaria poisoning in laboratory animals (Kay et al 1969); Cadmium fume pneumonitis (Carrington 1970); oxygen poisoning (Kistler et al 1967) and experimental lung disease induced by Freund's adjuvant (Faulkner and Esterly 1971). Alley and Manktelow (1971) have identified type 2 cell proliferation in some pneumonias of the sheep.

Bronchiolar epithelial cells have been found to line some alveoli in cases of diffuse fibrosing alveolitis of man (Spencer 1968) and cattle (Pirie and Selman 1972). This may be the result of extension of bronchiolar epithelium into the alveoli or even metaplastic change in alveolar cells. Nettesheim and Szakal (1972) demonstrated extension of bronchiolar epithelium, through membrane pores in the bronchiolar walls into adjacent alveoli, in mice chronically exposed to synthetic smog or CaCrO_4 dust. The term 'alveolar bronchiolisation' has been used to describe this lesion, in which cells which are of bronchiolar appearance come to line the alveolar surface (Nettesheim and Szakal 1972). 'Alveolar epithelial metaplasia' would express this less clumsily but some would interpret this to imply transformation of existing alveolar cells; this might not be the case.

Epling (1964c) described the ultrastructure of the lungs of cases of A.B.P.E. He concentrated on the lesion of emphysema and his results do not have any relevance to this study of the epithelium.

FOG FEVER: PROVOCATION TESTS WITH DICTYOCAULUS VIVIPARUS

1. Introduction
2. Materials and methods
3. Results
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FOG FEVER: PROVOCATION TESTS WITH DICTYOCAULUS VIVIPARUSINTRODUCTION

The aetiology of fog fever is not known but, in Britain, hypersensitivity to Dictyocaulus viviparus has often been suggested as a possible cause (Michel 1953, 1954; Smythe 1954; Downey 1968; Aitken and Sanford 1973). It was thought that this view was supported by the work of Michel (1954) who followed the response of calves to a lungworm infestation and observed their reaction to re-exposure to the same parasite at a later date. Acute clinical signs developed at certain periods during these procedures and Michel considered these to be the same as fog fever. Unfortunately, he did not demonstrate that the clinical responses were the result of pulmonary lesions consistent with fog fever, since the post-mortem findings were never published. The clinical criteria which were adopted were not diagnostic of fog fever either, so any association between the experimental results and fog fever was largely speculative. Weisman (1970), in Holland, experimentally infected animals which were said to be recovered cases of fog fever with lungworm larvae and claimed that further fog fever-like clinical signs could be produced after such a challenge.

The purpose of this study was to investigate the response of a group of animals which had been previously affected by fog fever to an experimental infection with lungworm larvae and to examine their lungs at post-mortem. Preliminary skin tests were used to determine the presence of skin sensitizing antibodies to D. viviparus, as an index of previous exposure to this parasite.

MATERIALS AND METHODS

Animals

The test animals (A-E) were seven adult beef suckler cows which were affected by fog fever during the autumn of 1972. These animals were purchased from their owners at the time of the original illness and maintained indoors on concentrates and hay until the start of this experiment. Significant points in the history of each animal are set out in tables (23,24). The diagnosis of fog fever was made after clinical and epidemiological examination in each case but in addition, in five of the seven animals, at least one other animal from the same farm had been examined clinically and at postmortem and found to be a case of fog fever. Animals A1 and A2 were from the same farm, as were D1 and D2. Control animals (F-L) were adult cattle admitted to the Veterinary Hospital with illnesses other than fog fever. Other controls were four month old parasite free calves which had been artificially reared indoors since birth.

Preparation of lungworm antigen

Adult lungworms were collected from the trachea and bronchi of clinical cases of parasitic bronchitis as soon as possible after slaughter. The worms were washed three times in phosphate buffered saline and then homogenized at room temperature in 25ml. of phosphate buffered saline in a Silversen tissue homogenizer for two to three minutes. The homogenate was then spun in cellulose nitrate tubes in the SW39 head of a Beckman L265B ultracentrifuge at 35,000 rpm. for 50 minutes. The resulting supernatant was collected and frozen at -20°C. in 1-2ml aliquots. Protein estimations were performed on each sample using the methods of Lowrey and Biuret (1951) and Daughaday (1952). The supernatant was used without dilution and as a 1 in 2 dilution in phosphate buffered saline as the antigen in the skin tests.

Skin Tests

0.1ml of lungworm antigen was injected into the shaven skin over the ribs using a tuberculin syringe and a 26 gauge needle. The area of swelling was outlined with a marker pen at 15 minutes, one hour, four hours and 72 hours after injection and subsequently measured with a ruler. Animals A-E were injected with lungworm antigen and with 0.1ml of phosphate buffered saline as a control injection in all cases.

Preparation of lungworm larvae

Third stage larvae of D. viviparus * were made up in 1 litre of tap water at 25°C.. After thorough agitation and stirring, 20 samples each of 0.25ml were placed on glass slides and examined under a Watson dissecting microscope. The total number of larvae present in each sample was counted and an average number present per millimetre was calculated; this was 492 larvae per ml. Animals A to E were given 60ml of this preparation containing approximately 30,000 larvae and calves M and N were each given 5,000 larvae (19ml) in order to check both the viability and infectivity of the larvae. The body weight of each animal is given in the table (25) along with the approximate number of larvae per kilogram.

Histology

The lungs of animals A to E and calves M and N were examined at postmortem when portions of tissue were taken from the lungs and bronchial tree and processed by the methods described earlier.

Haematology

Blood samples were taken into E.D.T.A. ** tubes from each animal (A-E) before larvae were administered in Experiment 2 and at weekly intervals thereafter until slaughter. Total white cell numbers were estimated using a Coulter Counter and the differential white cell count estimated from a stained smear.

* Allen & Hanbury Ltd. ** Ethylene - diamine - tetra acetic acid (EDTA)

Experiments

Experiment 1. Seven animals (A-E) were injected intradermally with 0.1ml of antigen A (lungworm antigen containing 12.9mg of protein per ml) and 0.1ml of antigen B (lungworm antigen containing 6.45mg of protein per ml) and 0.1ml of phosphate buffered saline.

Seven other adult control animals (F-I) and eight parasite free calves were also injected intradermally with the same preparations.

One week elapsed between the end of experiment 1 and the start of experiment 2.

Experiment 2. Seven adult cattle (A-E) were given 30,000 third stage larvae of D. viviparus orally and slaughtered one month later.

Two control calves (M and N) were each given 5,000 larvae and slaughtered one month later.

RESULTS

Skin Tests

The sizes of the skin swellings after intradermal injection of antigen A and B and saline are set out in table (26). The skin swellings were detectable 15 minutes after injection in most cases and reached maximal size over the succeeding one or two hours when they formed an irregular, flat plaque which disappeared gradually over 24 hours. No skin swellings were detected at 72 hours post injection.

Intradermal injection of saline alone did not produce any detectable skin thickening. No skin swellings were produced in any of the eight calves injected.

Clinical Signs

There were no significant clinical findings in animals A-E in the month following infection with larvae, and the respiratory rates of all animals decreased during this period (Fig.146). The two control calves, M and N, both exhibited severe signs of parasitic bronchitis, and M died shortly before the end of the experiment. The respiratory rates of M, N and two non-infected, environmental controls in the same pen are given in (Fig.147).

Haematology

The haematological findings in animals A-E are given in table (27). The samples taken on 23.11.72 were removed immediately prior to administration of larvae.

Postmortem Findings

The major pulmonary lesions are set out in table (28). Pulmonary lymphoid nodules were present in varying numbers and these were 2-3mm. diameter, round, grey foci which occasionally had a greenish centre. These raised nodules were most noticeable beneath the pleura in all lobes, but were also visible in the cut surface of the lung. Greenish-yellow, thick

mucous plugs filled some smaller bronchi and lay in the lumen of the lobar bronchi and trachea; many interlobular septa also had a greenish-yellow tinge. Interstitial emphysema was absent, though overinflation of the apical lobes was seen in a minority of animals. The main lesions in each animal are given in table (28). Subpleural pulmonary lymphoid nodules were counted in each case.

The mediastinal lymph nodes were grossly enlarged but the bronchial nodes were usually normal.

Pulmonary lymphoid nodules were found to be of two histological types. The first, which corresponded to the grey nodule with a greenish centre observed on gross examination contained a central mass of degenerating eosinophils intermixed with portions of brightly acidophilic parasitic remnants, giant cells and proliferating bronchiolar epithelial cells surrounded by active lympho-reticular cells infiltrated by many eosinophils. The second, the greyish nodule, was formed mainly of lympho-reticular cells, without an eosinophilic or germinal centre and contained fragments of parasites, portions of bronchial muscle and fewer eosinophils. Eosinophils were found in moderate numbers in the lumen of small bronchioles and in their lamina propria. Very many globule leucocytes could be distinguished in the bronchial epithelium and eosinophils were regularly found in the epithelium, in the lumen, in the lamina propria and occasionally around the glands also. There was a variable degree of infiltration of the lamina propria of the bronchial tree and the peribronchial connective tissue by cells of the lymphoid series and in one instance (D2) this was classed as heavy.

Mild focal pulmonary oedema was found in one animal in some of the sections examined. Eosinophils were infrequently noted in the alveolar lumen though infiltration of the alveolar and interlobular septa was often marked and these cells were commonly found in the perivascular and peribronchial connective tissue. Scattered lobules in the lungs of animal

A1 were very firm, white and diffusely infiltrated by a neoplasm which involved the mediastinal lymph nodes. These nodes were all greatly enlarged, very cellular and contained yellow, necrotic foci. This tumor was a carcinoma.

Longstanding infections of the liver by Fasciola hepatica were present in all animals, these were associated with fibrosis and calcification of the bile ducts and a variable degree of hepatic fibrosis, which was severe in animal A2.

Severe lesions of patent parasitic bronchitis were found in animals M and N; 1588 and 517 adult worms were recovered from the respective lungs.

ANIMAL	AGE	BREED	MONTH OF ILLNESS	OTHER ANIMALS EXAMINED AT POSTMORTEM
A1	7y	Hereford Cross	September	2
A2	Aged	Hereford Cross	September	
B	6y	Friesian	October	-
C	Adult	Blue grey	October	2
D1	2y	Hereford	November	2
D2	2y	Hereford Cross	November	
E	10y	Friesian	October	-

Table (23). Details of test animals that had recovered from fog fever.

ANIMAL	TIME (DAYS) FROM MOVE TO NEW PASTURE UNTIL :		
	ILLNESS	HOUSING INDOORS	LARVAL CHALLENGE
A1	4	42	61
A2	4	9	61
B	8	13	35
C	2	8	43
D1	6	9	17
D2	8	9	17
E	12	16	43

TABLE (24). Details of test animals that had recovered from fog fever.

ANIMAL	BODYWEIGHT/KG	LUNGWORM LARVAE/KG	TOTAL NO. OF LARVAE
A1	470	64	30,000
A2	510	59	30,000
B	472	64	30,000
C	268	112	30,000
D1	398	75	30,000
D2	371	89	30,000
E	406	73	30,000
Control calves M & N	-	-	5000

Table (25). The total numbers of larvae of Dictyoecaulus viviparus administered to 7 adult cows and two calves and the dose per kilogram bodyweight. The adult cattle (A-E) were recovered cases of fog fever and the calves were parasite free.

ANTIGEN	TIME AFTER CHALLENGE	DERMAL SWELLING (DIAMETER CM.) IN EACH ANIMAL													
		A1	A2	B	C	D1	D2	E	F	G	H	I	J	K	L
A	15min.	-	5	5	-	5	5	2.5	-	-	-	-	-	-	-
	120min.	5	8	5	4	7	5	5	2.5	-	-	-	-	2.5	-
	72hr.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B	15min.	-	5	5	-	4	4	-	-	-	-	-	-	-	-
	120min.	2.5	7.5	5	-	5	4	2.5	2.5	-	-	-	-	-	-
	72hr.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SALINE	15min.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	120min.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	72hr.	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table (26). The results of skin tests with Dictyocaulus viviparus antigens

in the 7 test animals (A-E) and 7 control cattle (F-L). Animals A-E were recovered cases of fog fever; animals F-L were adult cattle without clinical respiratory disease.

Animal	Pre-infection Sample 23.11.72			6 Days Post-infection 29.11.72			12 Days Post-infection 5.12.72			20 Days Post-infection 13.12.72		
	Total white Blood cells /cu.mm.	% Eosinophils	Total white Blood cells /cu.mm.	% Eosinophils	Total white Blood cells /cu.mm.	% Eosinophils	Total white Blood cells /cu.mm.	% Eosinophils	Total white Blood cells /cu.mm.	% Eosinophils	Total white Blood cells /cu.mm.	% Eosinophils
A1	n.s.	n.s.	8400	1.5	8,700	2	8900	2.5				
A2	6500	20	11,000	7.5	14,400	15	11,600	16				
B	16,200	14.5	16,200	24.5	15,700	9	15,500	24.5				
C	n.s.	n.s.	8000	4	8000	6.5	9,300	16				
D1	5300	2	7800	1	11,500	2	12,600	14				
D2	5000	1.5	8000	1.5	10,300	3	11,100	11				
E	5000	6.5	12,200	5	7000	4.5	4800	1.5				

Table (27) Haematological values in seven cattle given 30,000 lungworm larvae on 23.11.72. The cows (A-E) were

recovered cases of fog fever. (n.s. - no sample).

ANIMAL	PULMONARY LESIONS 28 DAYS AFTER INFECTION			
	BRONCHIAL MUCOUS PLUGS	PULMONARY LYMPHOID NODULES	INTERSTITIAL EMPHYSEMA	NUMBER OF LUNGWORMS RECOVERED
A1	++	8	-	-
A2	+++	40	-	-
B	+	16	-	-
C	++	36	-	-
D1	+++	10	-	-
D2	+	13	-	-
E	++	19	-	-
Control M	Marked consolidation, oedema and emphysema			1588
Control N	Moderate consolidation, oedema and emphysema			517

Table (28). Main pulmonary lesions in the test animals challenged with 30,000 larvae of Dictyocaulus viviparus (A-E) and 2 control calves given 5000 larvae. The test animals were recovered cases of fog fever and the control calves were parasite free.

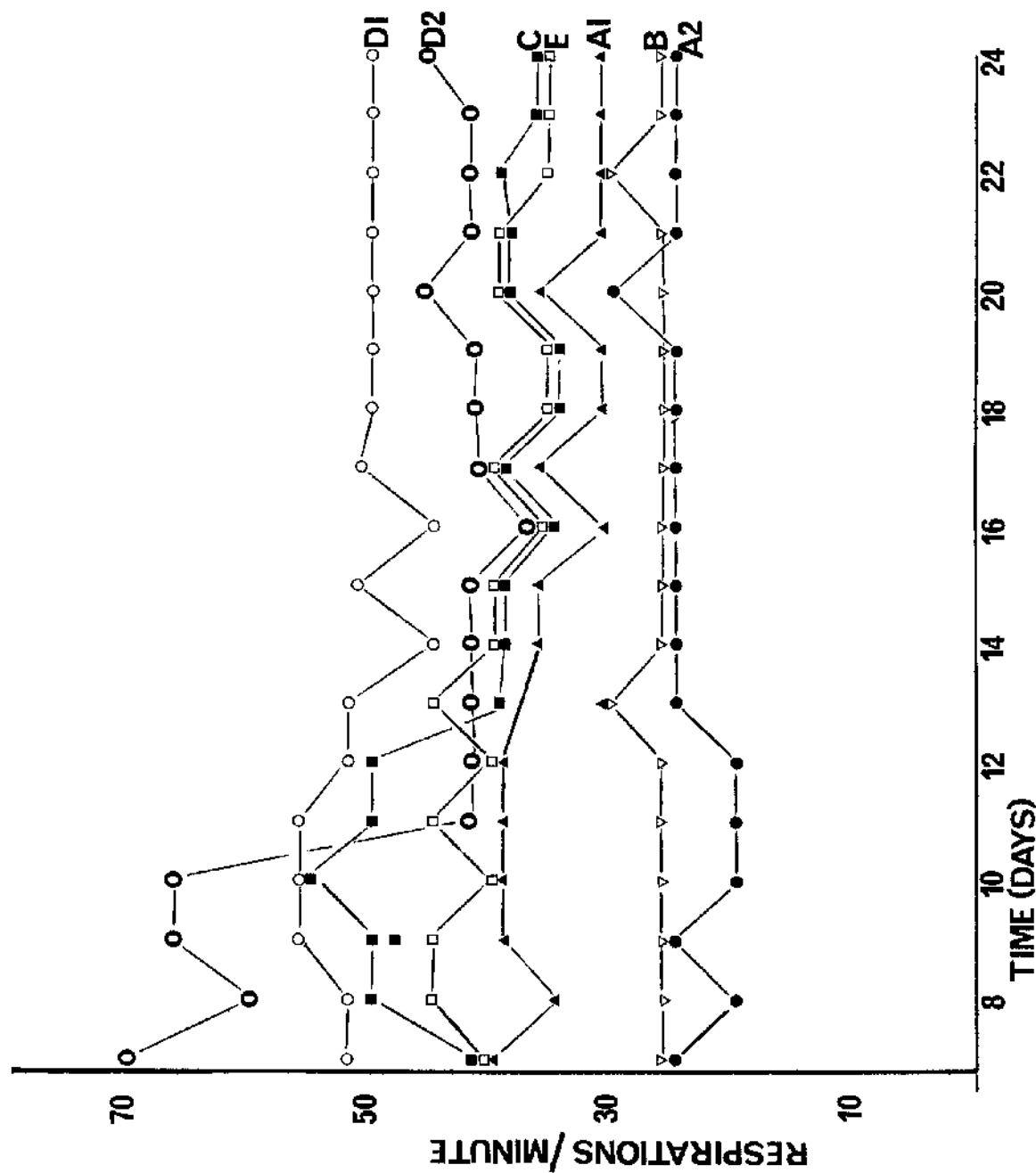


Fig.(146). Respiratory rates of 7 recovered cases of fog fever (animals A-E) from 7 days after challenge with 30,000 larvae of D. viviparus.

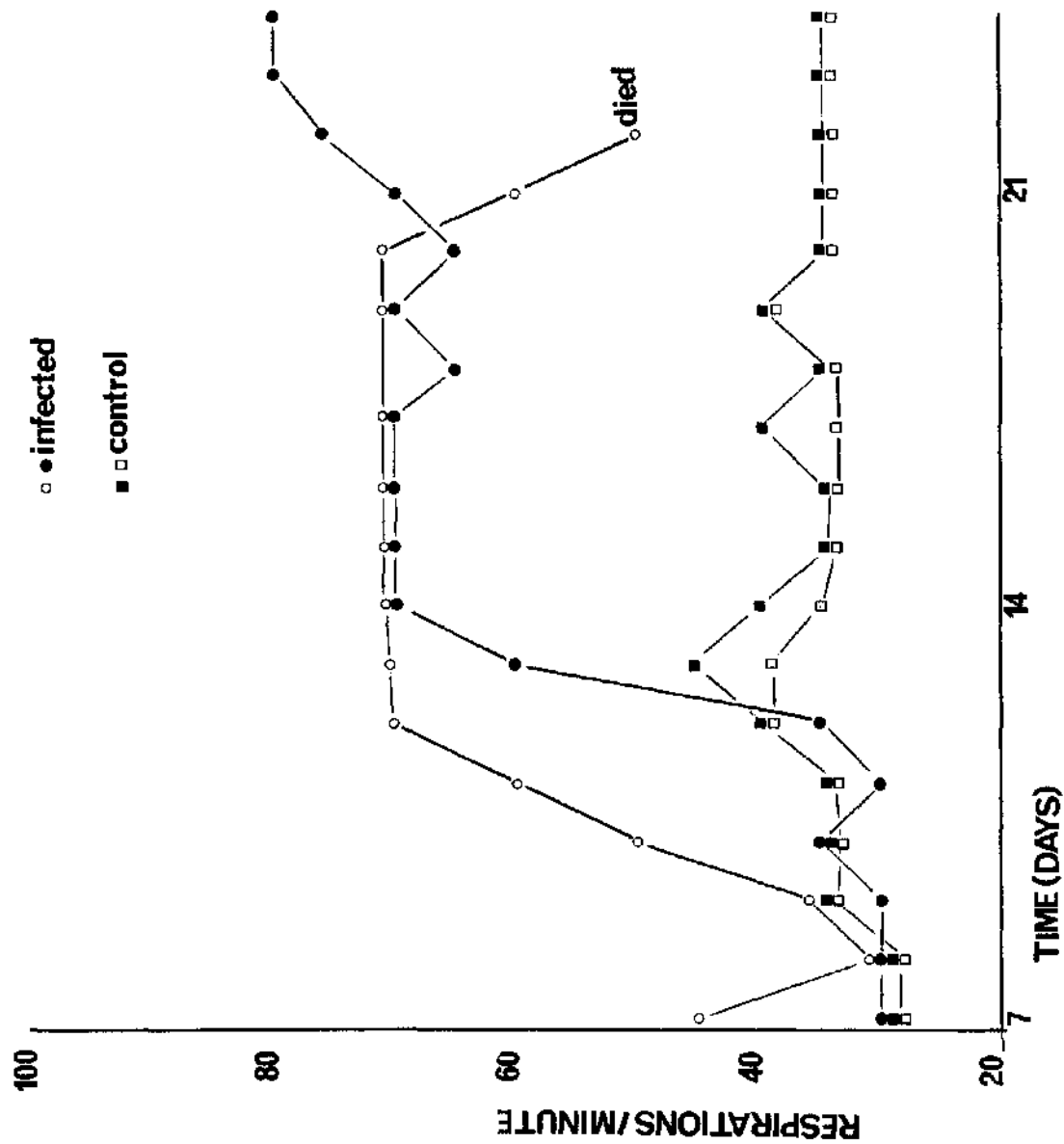


Fig. (147). Respiratory rates of 2 calves from 7 days after infection with 5,000 larvae of *D. viviparus* and of 2 parasite free environmental control animals.

DISCUSSION

If fog fever were a simple hypersensitivity reaction to lungworm larvae comparable to extrinsic allergic asthma of man, then the disease might well be expected to recur when the recovered animal was re-exposed to infective larvae. The results of this experiment indicate that this does not happen, even though skin sensitising antibodies are present. The pulmonary lesions after re-exposure were different from those of fog fever and similar to those of reinfection husk (Jarrett et al 1960; Jarrett and Sharp 1963 and Selman et al, to be published). Although the possibility that these animals developed fog fever initially as the result of a reaction involving lungworms cannot be discounted, it is clear that subsequently they appear to respond similarly to other animals repeatedly infected with D. viviparus (Jarrett and Sharp 1963).

Michel (1954) claimed to have produced fog fever when he reinfected calves with lungworm larvae after they had recovered from a primary infection. Jarrett and Sharp (1963) demonstrated that pulmonary lymphoid nodules were to be found in the lungs of reinfected calves and the lesions they described were not those associated with fog fever (Barker 1948; Leslie 1949). Some of the pulmonary signs described by Michel were almost certainly the result of such reinfection lesions; this type of reaction was described in field cases of husk by Jarrett et al (1960). It is also possible that these animals may have had pre-patent husk after the second infection, and this has also been noted by others (Poynter et al 1970).

Michel (1954) did not demonstrate that fog fever was involved in his experiment since the postmortem findings in the calves were not published and it is possible to explain the clinical signs in terms of husk alone. Recently, Roberts (1973) noted that Michel had modified his view that fog fever was the result of such infections.

Weisman (1970), in the Netherlands, infected 5 cases of "fog fever" after they had recovered, with 82,000 - 127,000 lungworm larvae on 3 or 4 separate occasions at intervals of 2-10 months. He made similar repeated challenges of normal calves after they had overcome a primary infection. "Fog fever" was said to follow many of these challenges and this disease was defined as "dyspnoea and an acute and fairly long lasting emphysema". The affected animals were not post-mortemed until several months after the clinical signs disappeared.

The relationship, if any, between this experimental syndrome and fog fever in Britain is obscure and the distinctions between the syndrome and reinfection husk are not apparent. The pulmonary lesions, in the five fog fever cases, were alveolar emphysema and oedema, generally of slight degree; hyaline membranes and alveolar epithelial hyperplasia were not mentioned. In the absence of post-mortem evidence to the contrary, these animals can only be regarded as exhibiting signs of reinfection parasitic bronchitis, since his clinical definition of fog fever cannot be held to be characteristic of that disease. It is unfortunate that the presence or absence of pulmonary lymphoid nodules was not recorded, since these are cardinal features of the reinfection phase.

Five animals (A1, A2, G, D1, D2) in our experiment were involved in outbreaks of fog fever in which at least one other animal was available for post-mortem diagnosis. In each case, the dead animal conformed to our diagnostic criteria for fog fever: it was an adult, beef-type cow that had developed acute onset respiratory distress after a recent move to better pasture and at post-mortem pulmonary oedema and hyaline membranes, interstitial emphysema and alveolar epithelial hyperplasia were found in the lungs. Two animals (B and E) were diagnosed as fog fever cases on clinical examination and epidemiological history alone.

The significant lesions in these seven animals were the pulmonary lymphoid nodules and the diffuse pulmonary eosinophilia, lesions comparable

to those described in reinfection husk (Jarrett et al 1960; Jarrett and Sharp 1963; Michel and Mackenzie 1965; Pirie et al 1971c; Selman et al, to be published). The pulmonary lymphoid nodules were of two types and one of these, which corresponded to the middle stage in development of the lympho-reticular, bronchiolo-occlusive lesion of Jarrett and Sharp (1963), was the result of our larval challenge. The mature, organised structure of the other lymphoid nodules suggested that these probably developed from an earlier larval intake on the farms of origin. Lymphoid nodules may persist for 3-6 months after formation (Pirie et al 1971c). The skin tests indicated that all these animals had experience of lungworm infection at some time prior to the start of this experiment. The absence of clinical signs after challenge and the small number of pulmonary lymphoid nodules indicates that these animals were to some extent immune and that the vast majority of the larvae were destroyed outwith the lung, possibly in the gut wall or in the mesenteric lymph nodes (Jarrett and Sharp 1963). It is not surprising that these adult cattle had a degree of immunity to parasitic bronchitis since many animals at grass in the autumn in the West of Scotland are exposed to lungworm larvae and it is not possible to categorically demonstrate that larvae are not present on any field regularly grazed by cattle. We were able to find larvae on the pasture grazed by animals A1 and A2 at the time they developed fog fever. Three parasite free calves were put on to this field for one month a few days after the fog fever incident began. At post-mortem on the day of removal, they were found to be affected by patent parasitic bronchitis and about 100 adult worms were recovered in each case. It is clear that A1 and A2 and the other fatal cases of fog fever on this farm were exposed to larval challenge at the time they developed fog fever, but the significance of this is not known.

We have not found pulmonary lymphoid nodules in a large series of cases of fog fever nor are the lesions in the cases comparable to those of

the early phase of reinfection husk (Jarrett and Sharp 1963; Pirie et al 1971c). Fog fever is not therefore the same process as the reinfection phenomenon described by Jarrett et al (1960).

Although globule leucocytes have not been described previously in cases of reinfection husk, they were very numerous in the bronchial tree of each animal examined. Histologically, some of the globule leucocytes appeared to be migrating into the epithelium but it remains uncertain whether all the cells present were the result of the current challenge since these cells are regularly found in fog fever and some may have persisted. Globule leucocytes are mast cells which have discharged their pharmacologically active contents (Miller, Murray and Jarrett 1967) and they are frequently found in parasitic infections, particularly in association with self-cure (Jarrett, Miller and Murray 1970). Their role in fog fever and parasitic bronchitis has not yet been described and their life span is not known.

There were no other significant lesions in the lungs of these seven cattle, in particular, fibrosis and alveolar epithelial hyperplasia were absent. There was no indication therefore, that any focus of "chronic fog fever" (Mackenzie 1966) remained, so it has not been possible to establish any link between fog fever and diffuse fibrosing alveolitis (Pirie and Selman 1972).

Fog fever has been considered to be the result of an allergy, sensitisation or hypersensitivity response in the lungs. The allergen involved was thought to be grass proteins (Barker 1948), spider's webs (Begg and Whiteford 1948) or D. viviparus (Michel 1953, 1954; Smythe 1954; Downey 1968; Weisman 1970) the results presented above do not deny lungworms any role in the pathogenesis of fog fever, but they contradict the claim that recovered clinical cases undergo further episodes of fog fever when exposed to lungworm larvae experimentally. Clinical reports have often incriminated lungworms in outbreaks of 'fog fever', but such claims

have mistaken the acute respiratory signs of uncomplicated parasitic bronchitis for fog fever and have implied, without proof, that the incidents were other than husk (Hudson 1951; Taylor 1951; Soliman 1952; Downey 1968; Crowther 1973).

Aitken and Sanford (1973) recorded positive Schultz-Dale reactions to lungworm antigens in the pulmonary veins of 3 cases of fog fever. The possible significance of this finding and the role of the pulmonary vein have been considered above, but only speculation is possible until complete, controlled investigations have been performed. Recovered cases of fog fever possess skin sensitizing antibodies to D. viviparus and their pulmonary veins may also respond to this antigen. In view of this, it is surprising that the administration of 30,000 larvae, six times the dose required to kill a calf, did not produce a clinical response. Some antigens must have reached the lung, since a proportion of the pulmonary lymphoid nodules in each case were the result of this larval challenge and the increase in the percentage of circulating eosinophils in animals A1, B, C, D1 and D2 was probably also due to this. The reason for the lack of clinical reaction is obscure, but it may be that 'blocking antibodies' which inactivated the antigens had developed. This possibility was not explored.

At the present time, there are no experimental results, either from our work or the reported findings of others, to support the idea that fog fever is a hypersensitivity reaction to oral reinfection by D. viviparus.

PULMONARY DISEASE INDUCED BY TRYPTOPHAN, 3 METHYL INDOLE
AND INDOLEACETIC ACID

1. Introduction and review of the literature
2. Materials and methods
3. Results
4. Discussion

PULMONARY DISEASE INDUCED BY TRYPTOPHAN
INDOLEACETIC ACID AND 3 - METHYL INDOLE

INTRODUCTION AND REVIEW OF THE LITERATURE

Johnson and Dyer (1966) reported a pulmonary disorder resembling acute bovine pulmonary emphysema (ABPE) in a group of steers given a single oral dose of the amino-acid tryptophan. In this experiment, eight animals were drenched with 250gms. (0.57gm per kg body weight) of the mixed isomers D, L-tryptophan and 5 of these died 1-7 days afterwards, when pulmonary emphysema was observed at postmortem.

This work was continued by Dickinson, Spencer and Gorham (1967), who administered single, oral doses of 0.5 - 0.6gm/kg of D, L-tryptophan to mature cattle of various breeds. In their first trial, three of four cows given such a dose developed progressive respiratory distress, which culminated in the death of one animal four days after dosage. The other two sick animals were examined at postmortem 12 days after treatment. The dead cow and one of those examined at postmortem were found to have 'severe' pulmonary lesions. The third affected animal, which had returned to normality before slaughter, had only microscopic lesions after death. The one animal without clinical signs throughout the trial was not slaughtered. A second experiment involving four more adult cattle resulted in all four developing degrees of respiratory distress, accompanied by pulmonary lesions of varying extent. A detailed description of the necropsy lesions was to be published; pulmonary oedema and hyaline membranes, pulmonary emphysema, alveolar epithelial hyperplasia and infiltration of the lungs by neutrophils and eosinophils were mentioned as the main findings.

These two reports indicated that a respiratory syndrome similar to that of A.B.P.E. could be produced by administration of tryptophan.

Carlson, Dyer and Johnson (1968) administered DL-tryptophan orally, by intra-peritoneal injection and by intravenous infusion to mature cattle and steers. Only the oral route resulted in clinical signs of respiratory disease, and these authors suggested that a metabolite of tryptophan, produced in the rumen, was the active principle. Carlson, Yokoyama and Dickinson (1972) found that a single oral dose of 0.35 - 0.4gm/kg of the D-isomer of tryptophan did not produce clinical disease in four steers, whereas the L-isomer, at 0.35gm/kg, induced pulmonary signs in two steers. L-tryptophan was converted mainly to 3-methyl indole (3MI), with some indole and indoleacetic acid, when incubated with rumen fluid from a hay-fed steer. D-tryptophan did not convert to these metabolites, whereas indoleacetic acid also formed 3-methyl indole after similar incubation (Carlson, Yokoyama and Dickinson 1972). Subsequently, these workers found that oral dosage of cattle with indoleacetic acid or 3-methyl indole, and intravenous infusion of 3MI led to pulmonary disease similar to that produced by L-tryptophan administration but more acute in onset. Pulmonary oedema and emphysema were the postmortem lesions in affected cows.

Eyre (1972b) measured the concentrations of 5-hydroxytryptamine (5HT) in the blood of calves given oral doses of L- or DL-tryptophan and claimed that this was sometimes elevated in the 5 days following treatment. He stated that two of the animals (aged 4-6 months) exhibited marked dyspnoea and respiratory distress and four other animals were affected to a lesser degree. Pulmonary emphysema of slight degree was observed in the lungs of the two dyspnoeic 4-6 months

old animals at necropsy, four days after treatment and in the lungs from two other affected animals (the author does not say which ones), whereas controls were normal. No histological examination was reported. Paradoxically, the two animals given the highest dose (1.0gm/kg D-L-tryptophan) did not develop clinical signs and their plasma 5HT levels were said to have remained within the normal range.

Monlux, Cutlip and Estes (1970) attempted to demonstrate a breed susceptibility to tryptophan induced lung disease. They dosed four animals of each of five breeds, Hereford, Jersey, Holstein, Angus and Shorthorn, with 0.6gm/kg tryptophan by the oral route (table 29). They concluded that Herefords were very susceptible, Jerseys less so and the other breeds not affected by this disease. The results of this breed differentiation study cannot be interpreted with any confidence because the figures are so small. Although the "breed susceptibility" propounded by the latter authors has been used to explain the frequent occurrence of A.B.P.E. or tryptophan induced disease in certain breeds (Dickinson and Piper 1971; Eyre 1972b) there is no proof that this is so. Most cases of A.B.P.E. were reported in Hereford, Angus and Holstein-Friesians or their crosses in Utah, but these breeds accounted for 97% of the beef type cattle in that state and Charolais, Brahma, Galloway, Ayrshires and their crosses were also affected (Blake and Thomas 1971). Dickinson, Spencer and Gorham (1967) recorded tryptophan induced disease in Guernsey, Shorthorn and Angus breeds at the same dosage level used by Monlux et al (1970).

Doses of the various isomers of tryptophan and the numbers and ages of the experimental animals used by the various workers are given in table (30), along with a resumé of the main results. The doses of 3 methyl indole and indoleacetic acid are given, with the corresponding data in table (31).

BREED	NUMBER OF ANIMALS	LUNG LESIONS AT POSTMORTEM
Hereford	4	<u>3 died</u> ; emphysema and adenomatosis 3-5 days after dosage. <u>1 killed</u> - no lesions
Jersey	4	<u>2 died</u> ; emphysema and adenomatosis 5-7 days after dosage <u>2 killed</u> - no lesions.
Holstein	4	<u>4 killed</u> , 2 had emphysema attributed to other causes.
Angus	4	<u>4 killed</u> , 1 had emphysema attributed to other causes.
Shorthorn	4	4 killed, no lesions.

Table (29) Breed susceptibility to tryptophan induced
emphysema.

(from Monlux, Cutlip and Estes 1970).

AUTHOR	NUMBER OF ANIMAL	AGE	DOSAGE	RESULTS
Johnson & Dyer (1966)	8	"steers"	1 oral dose 0.57g/kg D,L, tryptophan	$\frac{5}{8}$ animals died, 1-7 days afterwards.
Dickinson, Spencer & Gorhan (1967)	8	2-10y cows	1 oral dose 0.5-0.6g/kg D,L, tryptophan	1 died 4 days after dosage $\frac{5}{8}$ developed clinical disease.
Carlson, Dyer & Johnson (1968)	7	Mature cows	0.7g/kg D,L, tryptophan oral	4 died $1\frac{1}{2}$ - $4\frac{1}{2}$ days after dosage.
	4	"	0.7g/kg D,L, tryptophan and	No clinical signs
	3	"	0.35gm/kg Intraperitoneal injection	
	2	steers	20gm l/v infusion	
Monlux, Cutlip & Estes (1970)	20	7y aged cows	0.6gm/kg D,L, tryptophan	5/20 died.
Eyre (1972b)	2	4-6m	0.5g/kg L trypt.	2/2 severe signs
	2	6m	0.75g/kg D.L	2/2 moderate signs
	1	12m	0.5g/kg L	No reaction
	1	12m	0.5g/kg DL	" "
	1	12m	1.0g/kg DL,	No
	2	7-12m	1.0g/kg DL,	1 mild signs, 1 no response
	1	7-12m	1.0g/kg L	mild response
Carlson, Yokoyama & Dickinson (1972)	3	steers	0.4g/kg D	no response
	1	"	0.35g/kg D	" "
	2	"	0.35gm/kg L	2/2 pulmonary signs

Table (30) Summary of the responses obtained in experiments involving dosage of cattle with D and L isomers of tryptophan.

AUTHOR	ANIMALS	AGE	DOSAGE	RESULT
Carlson, Yokoyama and Dickinson (1972)	6	Cows	0.6gm/kg indoleacetic acid oral	3/6 developed severe clinical signs. 2/6 died.
	3	"	0.2gm/kg 3, methyl- indole, oral	All died
	2	"	0.1gm/kg 3, methyl-indole oral	Both developed clinical signs
	3	"	0.06g/kg 3, methyl-indole intravenous infusion	1 died, all 3 ill.

Table (31) Experiments with indoleacetic acid and 3-methyl-indole. The age and numbers of cattle involved, the dosages of chemical used and the results.

The aims of our studies were:

- 1) to reproduce the disease described by other workers in the U.S.A. and Canada.
- 2) to describe the pulmonary lesions of this disease and to compare them with those seen in fog fever and 'atypical interstitial pneumonia' in Britain.

MATERIALS AND METHODS

Animals All the calves used in these experiments were reared indoors on hay and concentrates from birth. One month before the experiment began, the daily concentrate ration was stopped. Eight calves had been given 2-4000 third stage larvae of D. viviparus 110-115 days previous to dosage with tryptophan, and were in the late post-patent phase of parasitic bronchitis. Four calves given oral tryptophan in experiment (1) were retained and used as part of the experimental group given 3 methyl indole in experiment (3) 14 weeks later.

Preparation of 3MI and tryptophan

The measured amount of 3MI or tryptophan was mixed with 2-3 gallons of water and administered, via a stomach tube, as a slurry.

Experiments

Ex. 1. 5 Hereford x Ayrshire calves, 10 weeks old, were given a single oral dose of D.L-tryptophan* (0.2gm/kg body weight) and 5 Hereford x Ayrshire calves of the same age were kept as controls.

* D.L-tryptophan - SIGMA Chemical Co.

Ex. 2.

Group A 5 Friesian x calves, 8-9 months old, were given a single oral dose of 0.5gm/kg L-tryptophan**, 110-115 days after a primary lungworm infection.

Group B 3 Friesian x calves, 8-9 months old, were similarly infected with lungworms but did not receive tryptophan; these were controls.

Exp. 3. Ten calves, all Hereford x, castrated males, age 6 months, were kept on a diet of hay, straw and some proprietary calf pencils for one month prior to dosage, and were then divided at random into 3 groups:-

- A. Four calves, 1-4, were given 0.2gm/kgm 3 methyl indole*** (3MI) in a single oral dose (these calves had received D,L, tryptophan at 10 weeks).
- B. Four calves, 5-8, were given 0.5gm/kgm L. tryptophan as a single oral dose.
- C. Two control calves, 9-10, were maintained on the same rations, but received no additional chemicals.

RESULTSEXPERIMENT 1

One animal in the experimental group became very tachypnoeic and hyperpnoeic 8 days after dosing and it was immediately slaughtered, along with a control animal which was tachypnoeic.

Severe 'cuffing' pneumonia and a secondary bronchopneumonia were the postmortem findings in the experimental calf. These lesions predominated in histological sections, but there were also foci of alveolar oedema, fine, eosinophilic hyaline membranes and alveolar

** L.-tryptophan - SIGMA Chemical Co.

*** 3 methyl indole (3MI) " "

epithelial cell proliferation. A small number of neutrophils and occasional eosinophils infiltrated such lesions and were also found in the alveolar septa and in the alveolar spaces. Large, foamy, alveolar macrophages were numerous in some alveoli. There was over-inflation of some acini, but no interstitial emphysema was recorded.

A milder degree of 'cuffing' pneumonia and a secondary bronchopneumonia were noted in the control animal, in which additional lesions were not apparent histologically.

None of the other animals exhibited any clinical signs attributable to the tryptophan dosage, so they were not slaughtered.

The clinical signs observed in the experimental and control calf were attributed to the 'cuffing' pneumonia and bronchopneumonia, exacerbated by particularly hot weather and poor ventilation in the calf pens at the time of the experiment.

EXPERIMENT 2

None of the calves in group A developed any additional respiratory signs attributable to tryptophan dosage during the 14 days following administration, so none of these were slaughtered.

One control animal died and at necropsy, a severe purulent bronchopneumonia and pleurisy were present; eight adult lungworms were found in the bronchi.

EXPERIMENT 3

Group A All four calves became ill after dosing with 3MI.

Animal (1) This calf was dull and anorexic immediately after dosage and two days later was markedly tachypnoeic (RR 130/min), coughed spontaneously and was dyspnoeic. The rectal temperature was elevated to 105°F.

Animals 2, 3 and 4 were dull, anorexic and tachypnoeic to a lesser degree than animal 1.

Animals 1 and 2 were slaughtered 48 hours after dosing; animals 3 and 4, 96 hours after treatment; the lungs were examined at postmortem.

Group B. Two calves exhibited mild clinical signs of tachypnoea and slight hyperpnoea; they were slaughtered at 6 and 7 days after dosage and examined at postmortem.

Group C. One animal from the control group was examined at necropsy on day 8.

Postmortem findings in animals 1 and 2 of Group A (table 32).

The lung lesions were similar in both calves, but more extensive in animal (1). Gross pulmonary oedema and interstitial emphysema, particularly in the diaphragmatic lobes, were noted in (1) (Figs. 148, 149), but these lesions were absent in (2). Many lung lobules, particularly in the apical lobes, were overinflated in both animals. Reddish-brown foci involving a portion of a lung lobule were found in all parts of both lungs of each animal. These foci were not depressed below the surface of the lung and on histological examination proved to be the result mainly of local pulmonary oedema. They were larger and more frequent in animal (1). The affected acini (Fig. 150) were filled by an eosinophilic protein precipitate, which was often formed into homogenous, eosinophilic hyaline membranes, lining the periphery of the alveoli and the alveolar ducts (Fig. 151). Alveolar macrophages, with indented nuclei and foamy eosinophilic cytoplasm, were found in moderate numbers in the alveolar spaces, along with many neutrophils. Intra-alveolar haemorrhage was occasionally seen in some acini. There was proliferation of the alveolar epithelial cells

in some oedematous alveoli and the cells were often bizarre in appearance (Fig. 153). Increased epithelial cell numbers were seen as short rows of 2-4 cells with hyperchromatic nuclei, one or sometimes 2 prominent nucleoli, and slightly basophilic cytoplasm, which was sometimes abundant. Mitotic figures were frequently seen in the free cells in the alveolar spaces, in the proliferating alveolar epithelial cells, and in the terminal bronchiolar epithelium, which was hyperplastic (Fig. 152). Alveolar septa were congested and slightly oedematous in such foci and there was a small increase in the number of interstitial cells. The interlobular septa were dilated by oedema fluid in the connective tissue and a moderate number of neutrophils, macrophages, plasma cells and lymphocytes was found in and around the lymphatic channels. A fine eosinophilic protein precipitate was noted in the bronchial and bronchiolar lumen, along with some neutrophils and macrophages. Many neutrophils were seen between adjacent epithelial cells and in the lamina propria of bronchi and bronchioles. Lymphocytes were also found intra-epithelially and in the lamina propria with plasma cells. There was a constant infiltrate of lymphoid and plasma cells in the peribronchial and peribronchiolar connective tissue; this infiltrate was sometimes arranged in aggregates; the 'cuffing' pneumonia lesions had largely regressed. Hyaline deposits were seen in the lumen of bronchioles; the epithelium of the terminal bronchioles was hyperplastic (Fig. 152) and the cells were sometimes bizarre. Globule leucocytes were not found in the bronchial tree.

Animals 3 and 4 (table 32)

Both sets of lungs were similar in appearance. Many lobules in all lungs contained red-brown foci and the discoloured area was not depressed below the lung surface. Histologically, similar lesions to those described in animals (1) and (2) above were seen, but alveolar epithelial hyperplasia was more advanced, focally. Some alveoli had a

complete epithelial lining of cuboidal cells with vacuolated apical cytoplasm (Fig. 154). Mitotic figures were frequent but the cells were more regular in shape than those seen in (1) and (2) and fewer bizarre cells were observed. Alveolar septa were often dilated by oedema and increased numbers of interstitial cells were apparent. Oedema and hyaline membranes were less pronounced. Many bronchioles were filled with macrophages and organising exudates. Interstitial emphysema was confined to a small area on the ventral surface of the left diaphragmatic lobe of animal (3).

Postmortem findings in animals 5 and 6 of Group B (table 33)

Many scattered reddish-brown foci were found in both lungs, these were the result of pulmonary oedema, hyaline membranes and alveolar epithelial hyperplasia (Fig. 155). The appearance of these lesions was similar to that in (3) and (4) above; eosinophils were more frequent in the alveoli in (5) and (6) and neutrophils were less common.

Control animal

Cuffing pneumonia affected the apical and ventral cardiac lobes in this animal.

ANIMAL	PULMONARY LESIONS
1	<p>Abundant white oedema fluid was found in the trachea and bronchi and moderate (2+) pulmonary oedema in the diaphragmatic lobes. Many petechiae were observed in the trachea and bronchi with fine intra-alveolar haemorrhages in some lung lobules. There was over-inflation of all lobes and moderate interstitial and subpleural emphysema of the diaphragmatic lobes. Many lung lobules were speckled reddish-brown in colour: on histological examination pulmonary oedema, hyaline membranes and proliferation of alveolar epithelial cells were found in such areas. Many alveoli contained numerous neutrophils and macrophages. There was bronchiolar epithelial hyperplasia and the bronchioles contained hyaline deposits, neutrophils and macrophages. Residual 'cuffing' pneumonia was noted in the apical lobes.</p>
2	<p>Many petechiae were found in the trachea and bronchi and there was occasional greenish-yellow mucous plugs in segmental bronchi. Reddish-brown portions in many lung lobules were found to have similar lesions to (1) above, but these were less extensive. Interstitial emphysema and gross pulmonary oedema were not seen. Residual cuffing pneumonia was noted in the apical lobes.</p>

ANIMAL	PULMONARY LESIONS
3	<p>A small number of petechiae were found in the trachea. Many lung lobules were speckled with red-brown foci, which were the result of pulmonary oedema, resolving hyaline membranes and focal alveolar epithelial hyperplasia, which was more advanced than (1) or (2) above. Subpleural and interstitial emphysema was confined to one area of 10 x 10cms. on the ventral surface of the diaphragmatic lobes, but most lung lobules were overinflated. Residual 'cuffing' pneumonia was present in the apical lobes.</p>
4	<p>Many red-brown foci were noted in the lung lobules similar to those found in animal (3). Interstitial emphysema was not recorded but there was overinflation of many lung lobules. Residual 'cuffing' pneumonia was recorded in the apical lobes.</p>

Table (32) Pulmonary lesions in four calves dosed with
3, methyl-indole (0.2gm/kg body weight)
48 hours (1 and 2) and 96 hours (3 and 4)
before slaughter.

ANIMAL	PULMONARY LESIONS
<p>5 . Killed on day 7.</p>	<p>A small number of petechiae were found in the trachea and bronchi. Most lung lobules were overinflated and a minority of lobules in all lobes were speckled red-brown in colour; in these areas there was focal pulmonary oedema and hyaline membranes, which were resolving, and alveolar epithelial hyperplasia. Alveolar septa were dilated and oedematous; interstitial cells were increased in number. Neutrophils and eosinophils were found in the alveolar spaces and alveolar septa. Bronchiolar epithelium was hyperplastic; the bronchioles contained hyaline deposits and organising intra-bronchiolar exudates. Interstitial emphysema was absent and pulmonary oedema was minimal.</p>
<p>6 Killed on day 8.</p>	<p>No petechiae were found in the trachea and bronchi. A small number of lobules in all lung lobes were reddish-brown in colour and were found to be similar to (5) histologically. There were scattered lung lobules associated with lesions of 'cuffing' pneumonia in the apical lobes.</p>

Table (33) Pulmonary lesions in two calves killed 7 and 8 days after a single oral dose of 0.5gm/kg L-tryptophan.

DISCUSSION

The pathology of the pulmonary disorders induced by oral dosage of cattle with 3MI or L-tryptophan has been poorly documented in published papers. Pulmonary lesions of oedema, hyaline membranes, overinflation of alveoli, interstitial emphysema and proliferation or hyperplasia of alveolar epithelial cells were found focally in the animals of groups A and B in experiment 3. These findings were comparable to those described by others after D,L-tryptophan (Dickinson, Spencer and Gorham 1967), L-tryptophan and 3MI administration (Carlson, Yokoyama and Dickinson 1972; Dickinson and Piper 1971).

These lesions were similar in nature, but not in degree, to those found in cases of fog fever in beef cattle and atypical interstitial pneumonia in indoor calves during our survey. With one exception, the lungs of our 3MI or L-tryptophan treated calves contained only focal lesions and these were much less than the diffuse, dramatic lesions of fog fever. 'Severe pulmonary emphysema and adenomatosis' have been described in adult cattle fed D,L-tryptophan (Monlux, Cutlip and Estes 1970) but, unfortunately, no indication of the method used to grade these lesions was given. Our experimental cases lacked some of the features of fog fever histologically: neutrophils were frequently found and eosinophils were uncommon; giant cells were absent and globule leucocytes not apparent in the bronchial tree. Eosinophils, but not globule leucocytes, have been described in 3MI and tryptophan induced lung disease (Dickinson and Piper 1971). The neutrophilia observed in some instances in our animals may have been the result of the concurrent cuffing pneumonia and mild bronchopneumonia, which was always present; the use of older experimental animals would minimise this complication.

Since the original observations with D.L-tryptophan, it has been shown that L-tryptophan is the active isomer in the induction of lung disease and that L-tryptophan can be converted by rumenal micro-organisms, in vitro, to 3 methyl indole (Carlson, Yokoyama and Dickinson 1972). This latter compound was more effective and more rapid than L-tryptophan in producing pulmonary disease after oral treatment of cattle. The active metabolite, produced from L-tryptophan in the rumen, is probably 3MI, since this is effective when given intravenously, whereas L-tryptophan is not (Carlson, Dyer and Johnson 1968 and Carlson, Yokoyama and Dickinson 1972).

The mode of action of 3MI or L-tryptophan is not known, but there is an hypothesis that 3MI is liberated from ingested herbage or L-tryptophan in the rumen and acts, possibly via a metabolite, on the lungs to produce A.B.P.E. or fog fever.

Carlson, Yokoyama and Dickinson (1972) suggested that 3MI, or an indole derivative, disrupted cellular membranes in the lungs and that this was involved in the aetiology of pulmonary emphysema in animals and possibly man. The "pulmonary emphysema" described in tryptophan and 3MI induced lung disease has never been qualified, but was presumably interstitial. There has been no indication that centrilobular or panacinar emphysema, comparable to these destructive lesions in man, were found.

Eyre (1972b) claimed he had found elevated 5HT levels in the blood of some cattle given either L- or DL-tryptophan and raised the possibility that 5HT might be the active compound in this type of lung disease. The action of serotonin (5HT) in cattle has been studied in most detail in relation to anaphylaxis. Serotonin (5HT), which is present in blood platelets, is formed from the precursor tryptophan by the enzymes tryptophan-5-hydroxylase and 5-hydroxy-tryptophan-decarboxylase.

The techniques used to measure blood serotonin levels are delicate, since serotonin may be liberated from damaged platelets during blood collection. Although the bronchi, pulmonary artery and pulmonary vein are sensitive to 5HT in cattle (Aitken and Sanford 1970; Eyre 1970, 1971a), pulmonary lesions comparable to those induced by 3MI or L-tryptophan have not been described after serotonin administration. Specific antagonists to 5HT and histamine did not protect cattle undergoing anaphylactic shock and it was suggested that neither 5HT nor histamine were important in bovine anaphylaxis (Aitken and Sanford 1969a; Alexander Eyre, Head and Sanford 1970). Eyre (1972a) has retracted from this view and proposed that 5HT, histamine, dopamine, slow reacting substance, plasma kinins and possibly prostaglandins were involved in this reaction. The role of serotonin in anaphylaxis is not understood, but it does not seem likely that it is the only factor involved. The implication of serotonin in tryptophan induced disease is a speculation: the anaphylaxis studies have not provided any useful parallels.

The lack of respiratory signs after administration of D. L-tryptophan in experiment 1 may have been the result of immaturity, possibly in rumen function, of these calves, which were younger than any used by other workers. However, the pulmonary lesions in the one calf examined, though slight, were consistent with those described in the further experiments; so it may be that histological examination of the other animals would have revealed similar lesions.

It was hoped that dramatic clinical signs and diffuse pathological lesions would develop in the animals treated in the post-patent phase of parasitic bronchitis; these were not observed.

There is no doubt that administration of DL- or L-tryptophan or 3MI to cattle can result in lesions which, if widespread, would be comparable to those of fog fever. There has been no demonstration, so far, that these compounds are present in aftermath or similar pasture at a significant concentration to be dangerous. This may be partly the result of difficulties in analysis. Tucker and Maki and Maki and Tucker (1962) did record experimental indication of A.B.P.E. in association with pasture change: tryptophan or indole levels in the grass and the presence of lungworms were not investigated.

ACUTE RESPIRATORY DISTRESS AND BORDETELLA PERTUSSIS

1. Introduction
2. Materials and methods
3. Results
4. Discussion

ACUTE RESPIRATORY DISTRESS AND BORDETELLA PERTUSSISINTRODUCTION

Reaginic antibodies are the mediators of immediate hypersensitivity reactions (type 1 hypersensitivity) and are believed to be responsible for many allergic diseases such as hay fever and extrinsic allergic asthma. Reaginic antibody in man is found in the immunoglobulin class IgE, but in the cow reaginic antibody is in the class IgG, although this may yet be separated further with more sophisticated techniques. Reagins attach to mast cells and after interaction with the antigen bring about the release of vasoactive chemicals, such as histamine and slow reacting substance A (S.R.S.A.).

The production of reaginic antibodies is a common result of helminth infections and then these antibodies are frequently present in large amount. It has been suggested that reaginic antibodies are important in mediating the 'self-cure' in parasitic infections, although not all workers agree on this point (Murray 1972). Many of the ideas about this reaction have come from experimental studies with Nippostrongylus brasiliensis, a parasite found in the small intestine of the rat. The gut is the main shock organ in this species (Sanyal and West 1958).

Reaginic antibodies to Dictyocaulus viviparus are present in the sera of animals which have been affected by parasitic bronchitis and may also be found in the sera of cases of fog fever (unpublished observations). The main shock organ in the cow is believed to be the lung (Aitken and Sanford 1969a, Eyre et al. 1973).

It is very likely that reaginic antibodies are involved in the 'self-cure' reaction in parasitic bronchitis and it is also possible that they may be involved in the pathogenesis of the lesions

of complicated post-patent husk. Interstitial emphysema, pulmonary oedema and hyaline membranes and severe, diffuse alveolar epithelial hyperplasia are the main pulmonary lesions in complicated post-patent husk and also in fog fever. The aim of this study was to induce reaginic antibodies to D. viviparus in cattle and then to impose a 'self-cure' response. It was hoped that pulmonary lesions consistent with fog fever and complicated post-patent husk would ensue. Reaginic antibodies to D. viviparus were to be induced by the use of antigens derived from lungworms together with the adjuvant Bordetella pertussis, to avoid complications from the natural self-cure reaction which would result from infestation with live parasites.

Reaginic antibodies have been produced in rats by sensitisation with antigen and B. pertussis suspension (Moto 1964). In addition to this adjuvant effect on antibody production, suspensions of B. pertussis have other properties such as : increasing the animal's susceptibility to histamine, serotonin, active and passive anaphylaxis and cold stress. Hyperleukocytosis, predominantly the result of lymphocytosis, follows intravenous injection of the suspension (Morse 1965; Munoz and Bergman 1968; Morse and Bray 1969).

Before attempting to enhance reagin production in cattle with B. pertussis, a preliminary investigation was made into the haematological changes after the use of the suspension. The results of this experiment are described below. It was hoped to establish a suitable dose of the suspension for reagin potentiation by comparing the haematological changes in the cow with those of other animals.

MATERIALS AND METHODS

Animals All the experimental animals were Friesian cross calves aged 5-6 months. They were housed indoors from birth and maintained on a ration of hay and concentrates. None of the animals had ever been at grass and all had recovered clinically from a respiratory infection during the period when they were 3-5 months of age. The calves were divided into two groups:-

Group 1: Calves A-E were five control animals maintained in a similar environment and manner to group 2.

Group 2: Calves F, G, H, J and K were given 25ml of B. pertussis * suspension by slow intravenous injection on day 6 of the experiment. Calf J was slaughtered on humane grounds on day 10. Calf G was slaughtered on day 13 and calves F, H and K on day 20. All the animals were examined at postmortem.

Haematology At specified intervals, blood samples were taken from the jugular vein into bijou bottles containing E.D.T.A.**. Total white cell numbers were estimated by the use of a Coulter counter type B*** and differential counts of 400 cells were made on Leishman stained smears taken from each sample.

Samples on days 1 and 3, and the first sample on day 6 were taken before injection of B. pertussis suspension. The second sample on day 6 was at 2 hours post-injection and the third at 6 hours.

Histopathological techniques

Tissues were fixed, processed and stained as specified in the general materials and methods section.

* Bordetella pertussis suspension (8×10^{10} organisms/ml) Burroughs Wellecome Co.

** Ethylene-diamine-tetra-acetic acid. *** Coulter Electronics Inc. Florida USA.

EXPERIMENT

The purpose of this experiment was to compare the haematological values in the control and experimental groups to determine if and how B. pertussis would influence these parameters.

RESULTS

Haematology The results of the haematological examinations of group 1 are given in table (34). The numbers of circulating neutrophils and lymphocytes in the animals of group 2 are set out in figures (156, 157).

In the animals of group 1, the ratio of neutrophils to lymphocytes remained relatively constant at approx. 1 : 3 throughout the experimental period. Total white cell numbers in each case fluctuated within normal limits from day to day.

The ratio of neutrophils to lymphocytes and the total white cell count of each animal in group 2 were comparable to those of animals in group 1, until the injection of B. pertussis on day 6. Two hours after injection, the number of circulating lymphocytes fell dramatically from 7,800-8,600 cells/cu.mm. to between 1450 and 2150 /cu.mm.. Six hours after injection, the numbers had risen slightly to between 2100 and 3000/cu.mm.. On day 7, the number of lymphocytes in each case was at or above the level before injection and remained at this for the succeeding days. There was a slight lymphocytosis in animals F, G and H.

The numbers of circulating neutrophils in each animal of group 2 fell markedly by 2 hours post-injection on day 6 from 2100-5200 cells/cu.mm. to 42-220 cu/mm. Numbers increased rapidly thereafter;

at six hours the range was 600-1900 cu/mm. and 24 hours later, on day 7, 9000-18000 cu/mm.. Numbers declined after this and returned to approximately pre-injection levels by day 10 (animals F,G, and K). At this time animal J had a neutrophilia.

Clinical signs Group 1: all the calves in this group remained clinically normal throughout the trial period. None were slaughtered.

Group 2: all the calves in this group were clinically normal during the month prior to the experiment.

Thirty minutes after injection of the B. pertussis suspension on day 6, they were all dull and slightly tachypnoeic. Two hours after injection, all were markedly tachypnoeic (respiratory rates 80-90 per minute) and hyperpnoeic and several grunted on expiration. Copious, clear nasal discharge was observed in two animals (J and K). The clinical signs were less dramatic four hours after injection and abated completely over the next 24 hours. Animal (J) suddenly relapsed on day 9 and there was renewed tachypnoea and hyperpnoea; the calf deteriorated over the next 24 hours and became severely dyspnoeic. Animal (J) was slaughtered on humane grounds on day 10, 96 hours after injection. The remaining four animals were clinically normal on day 10 and were slaughtered 7 days (animal G) and 14 days (F,H and K) after injection, without developing any additional clinical signs.

Pathology Animal (J). The lungs were deep red-purple in colour, with the exception of the dorsal part of the apical lobes, which was pale pink and overinflated. Almost the entire lung (Figs.158,159) was very rubbery in consistency and the cut surface of each lobule was smooth and glistening. Little gas could be expressed. Pulmonary oedema

was of moderate degree in all lobes and many yellow, gelatinous oedema strands were observed in the interlobular septa. Severe, extensive interstitial emphysema was present and there were large gas bullae in the diaphragmatic lobes, with extensive perivascular and peribronchial gas dissection. The appearance and texture of the lung were consistent with severe, diffuse, alveolar epithelial hyperplasia with pulmonary oedema and hyaline membranes. A moderate volume of white, frothy fluid and numerous petechial haemorrhages were noted in the trachea and bronchi. An organised pleurisy had resulted in adhesions between the left diaphragmatic and cardiac lobes. Many petechial haemorrhages were found on the epicardium and endocardium. The bronchial and mediastinal lymph nodes were much enlarged and oedematous; small gas bullae were present in the mediastinal nodes.

Severe alveolar epithelial hyperplasia (grade 3+) was the main lesion in multiple histological sections from all lobes of both lungs (Fig. 160). All alveoli were lined by a continuous layer of cuboidal cells resembling type 2 pneumocytes (Figs. 162, 163). Large mononuclear cells accumulated in the alveolar spaces and there were heavy deposits of hyaline material, infiltrated by macrophages and neutrophils, and thick hyaline membranes in alveoli and alveolar ducts (Fig. 163). Alveolar septa were dilated (Fig. 163) by oedema fluid and increased numbers of large mononuclear cells, probably interstitial cells or blood monocytes, with neutrophils and some eosinophils. Plasma cells and lymphocytes were uncommon and alveolar septal fibrosis was absent. Macrophages, neutrophils and some eosinophils were found in the lumen of the bronchioles, with hyaline deposits. There was oedema of the lamina propria of the bronchioles and bronchi. Globule leucocytes were not present in the bronchial epithelium. There was a heavy peribronchial, peribronchiolar and

perivascular infiltration and accumulation of lymphocytes with plasma cells in the apical lobes and frequent germinal centres had formed (Fig.161). Lymphocytes and plasma cells were also very numerous in the lamina propria of the bronchi in this lobe and germinal centres had occasionally developed.

Animals F,G,H and K

The main findings in the lungs of all four animals were extensive lesions of 'cuffing pneumonia'. There was collapse of most lobules in the anterior half of the lungs and marked peribronchial and peribronchiolar cuffing. Histological examination revealed the presence of large lymphoid cuffs with marked germinal centre formation in the perivascular, peribronchial and peribronchiolar tissue (Figs. 164, 165). These lymphoid cuffs appeared to be particularly well developed. Alveolar epithelial hyperplasia, pulmonary oedema and hyaline membranes and interstitial emphysema were absent.

ANIMAL	NUMBER OF NEUTROPHILS (N) AND LYMPHOCYTES (L) PER CUBIC MILLIMETER OF BLOOD ($\times 10^3$)																	
	N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L
A	2.45	6.65	3.2	5.6	3.1	5.3	2.7	5.2	3.3	5.4	3.0	6.9	2.3	6.3				
B	2.85	9.55	2.75	6.75	3.2	7.9	3.5	7.4	3.0	7.3	2.9	8.5	4.3	8.5				
C	1.5	7.9	2.3	5.7	2.0	6.5	2.6	6.1	2.0	6.0	3.6	7.5	3.7	7.1				
D	5.3	7.0	4.1	6.7	5.4	7.5	5.8	7.1	5.5	7.4	3.7	7.4	5.4	7.1				
E	4.8	7.5	3.3	8.2	3.7	7.5	5.1	7.3	3.6	7.7	4.3	7.3	3.7	8.0				
DAY	1		3		6a		6b*		7		8		9					

* this sample was taken 6 hours after the routine sample 6a.

(Contd.)

ANIMAL	NUMBER OF NEUTROPHILS (N) AND LYMPHOCYTES (L) PER CUBIC MILLIMETRE OF BLOOD ($\times 10^3$)											
	N	L	N	L	N	L	N	L	N	L	N	L
A	2.2	5.8	2.2	6.3	3.1	6.6	3.2	7.5	3.5	7.2	3.6	7.0
B	2.9	7.1	2.3	7.9	3.1	6.0	4.1	7.3	3.5	7.5	3.4	7.6
C	3.7	7.0	3.2	6.5	3.7	6.2	4.1	7.0	3.3	5.5	3.1	5.6
D	3.7	6.0	3.3	8.1	3.6	5.5	4.4	6.7	4.0	6.5	4.5	6.7
E	3.8	9.0	2.2	7.0	3.2	5.7	3.6	7.5	3.6	7.3	3.7	7.5
DAY	10	11	12	13	15	16						

Table (34) The numbers of neutrophils and lymphocytes per cubic millimetre of blood in 5 control calves (A-E) from days 1-16 of the experiment.

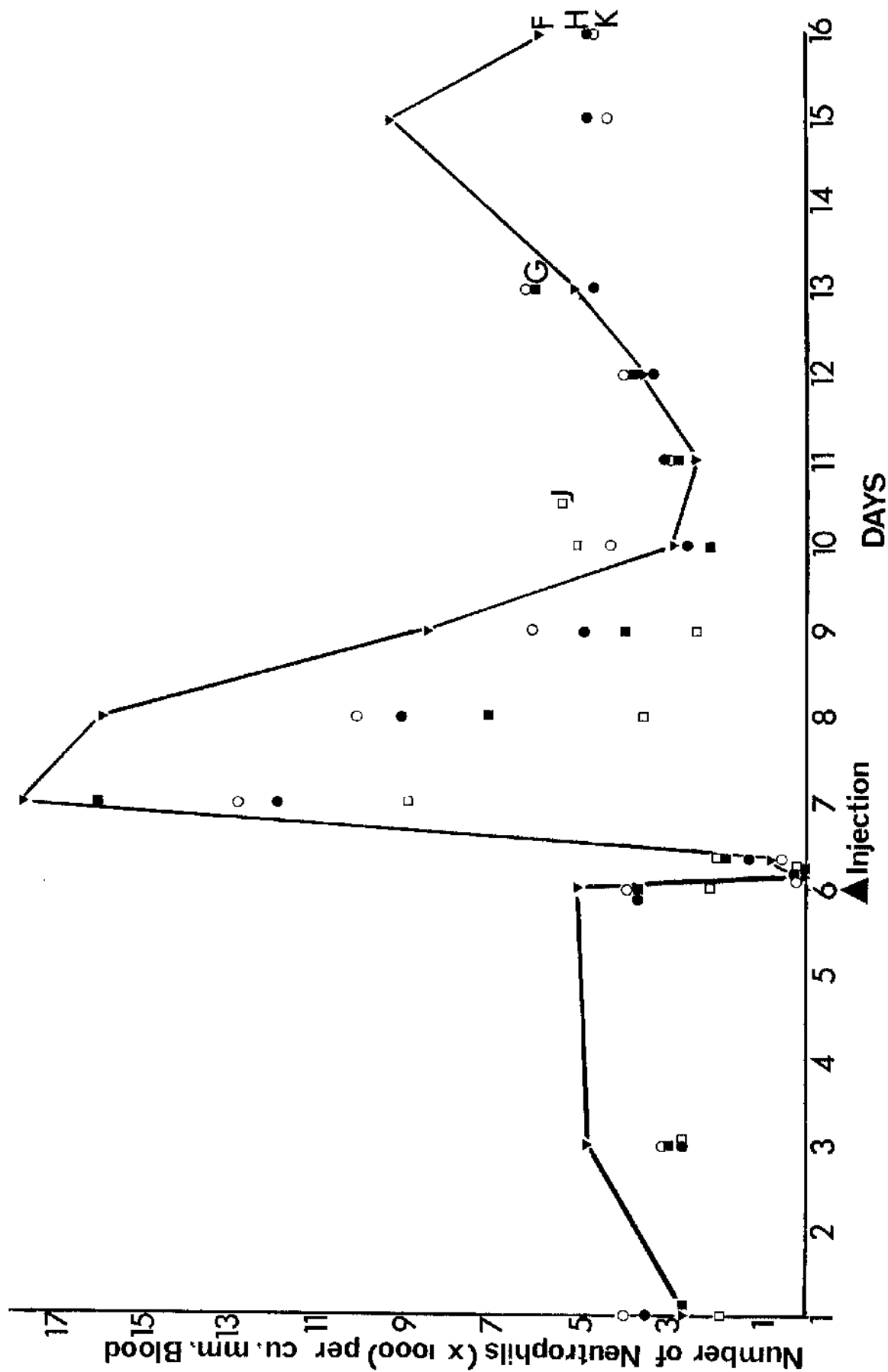


Fig. (156). Numbers of neutrophils per cu. mm. of blood in 5 calves (F-K) given Bordetella pertussis suspension on day 6 of the experiment.

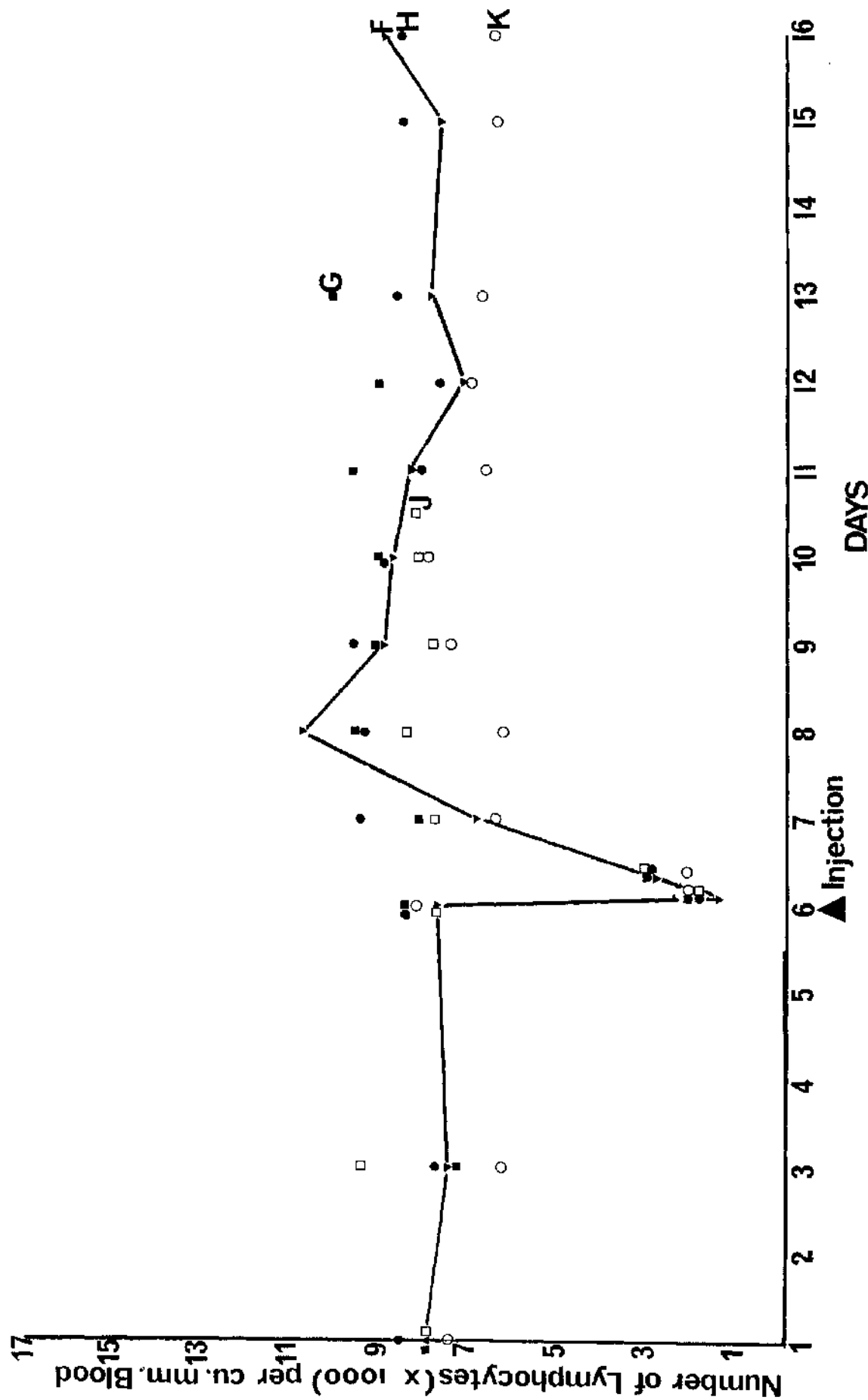


Fig. (157). Numbers of lymphocytes per cu. mm. of blood in 5 calves (F-K) given Bordetella pertussis suspension on day 6 of the experiment.

DISCUSSION

There were two interesting results from this experiment: the haematological changes in calves (F-K) and the acute respiratory distress syndrome in calf (J).

Rai et al (1971a) investigated the response of calves to intravenous injection of the supernatant fluid from liquid medium cultures of phase 1 B. pertussis organisms. Calves of 100kg. body weight were given a dose of supernatant which varied from 0.002-1.00 ml/kg. Doses of 0.05 ml/kg and above were effective in producing lymphocytosis but also caused deaths, which were attributed to "anaphylactoid respiratory distress". The concentration of the pertussis supernatant is not directly comparable to that of the material used in this study. Rai et al (1971a) stated that the supernatant was recovered by centrifugation of a culture of B. pertussis of up to 2×10^{10} bacilli/ml.. A calf of 100kg, given 0.05ml/kg would receive 5ml of the supernatant, representing the products of 1×10^{11} organisms. The calves (F-K) in this trial were given 25ml of pertussis vaccine, a mixture of organisms and 'supernatant', at a concentration of 8×10^{10} organisms/ml: that is a total of 2×10^{12} organisms and their products. Since calves F-K were 150-200kg in weight, this represented an individual dose of approximately 1×10^{10} organisms/kg body weight.

Rai et al (1971a) found that in the first 60 minutes after intravenous injection of pertussis supernatant the numbers of blood neutrophils and lymphocytes dropped markedly before beginning a 2-4 fold increase in numbers. The lymphocytosis was maintained for at least 16 days, whereas the neutrophil count rapidly returned towards normal over 8-9 days. Rai et al (1971a) recorded a peak neutrophil count of 14,000 cells/cu.mm. in one calf on the second day after

injection. The maximum neutrophil count in the results given here, 18,000 cells/cu.mm., was noted in animal (F) 24 hours after injection: blood neutrophil numbers in all calves had largely returned to pre-injection levels by the fourth day after injection. The peak response and return to normal occurred earlier than had been observed by Rai et al (1971a). Maximum blood lymphocyte numbers were discovered 24 (H and K) to 48 (F, G and J) hours after injection: the range was of 6500-10,800 cells/cu.mm.. Rai et al (1971a) demonstrated a maximum blood lymphocyte count of 19,000 cells/cu.mm. 2-3 days after injection, and this count remained elevated for 16 days, during which time the number decreased to 7,000 cells/cu.mm.. The blood lymphocyte count in calves (F-K) declined to pre-injection levels in the 7 days after dosing. The maximum blood lymphocyte count and the duration of the lymphocytosis were less in calves (F-K) than those in the one calf said by Rai et al (1971a) to be representative of the group.

The discrepancies between this report and that of Rai et al (1971a) are impossible to explain fully, since the pertussis vaccine used here and the pertussis supernatant used by Rai et al differ in composition, although both contain lymphocytosis promoting factor (L.P.F.) (Morse and Bray 1969). Differences may perhaps be related to dose, although it should be noted that maximum lymphocytosis in the mouse was provoked by a dose of 1.5×10^{10} organisms intravenously (Phanuphak et al 1972). If the body weight of the mouse were 30gm., the equivalent dose per kilo of body weight would be 50×10^{10} organisms. The dose used in the calves (F-K) was 1×10^{10} organisms/kg body weight. Comparisons of doses in different experiments are complicated by the fact that supernatant fluid from cultures is up to 50 times more active than the bacterial cells alone in promoting lymphocytosis (Morse and Bray 1969). However, it is interesting that Phanuphak et al (1972) observed that a dose of 1.5×10^{10} organisms was more effective

than a lower (5×10^9) or higher (3×10^{10}) one in inducing lymphocytosis, since there was less leukocytosis with the latter two dose regimes and the percentage of lymphocytes did not vary significantly from normal. This would suggest that the dose given to calves (F-K) was not the optimal one for provocation of lymphocytosis.

Rai et al (1971a) recorded several deaths in calves and sheep given intravenous pertussis supernatant and considered these to be the result of "anaphylactoid respiratory distress". These authors were interested in the kinetics of the lymphocytes and did not describe the pathology of fatal cases or state what was meant by 'anaphylactoid'. Rai et al (1971b) claimed that the endotoxin of B. pertussis was responsible for the marked leukocytopenia involving the neutrophils and lymphocytes during the first hour after injection. It is interesting that calves undergoing anaphylactic shock exhibit a profound leukopenia involving the neutrophils and a thrombocytopenia (Dungworth 1965; Wray and Thomlinson 1969). It is possible that the clinical response noted by Rai et al (1971a) and the signs in calves (F-K) shortly after injection were caused by B. pertussis endotoxin. Osbourne and Smibert (1964) reported "anaphylactoid" deaths in calves after intravenous administration of supernatant from a Vibrio foetus culture. Blake (1965) investigated the effects of V. foetus endotoxin in the lungs of sheep. He recorded clinical signs of hyperpnoea and dyspnoea, beginning within minutes of injection and reaching a peak after 4 hours. At postmortem, 24 hours after injection, pulmonary oedema and emphysema were noted. Such 'endotoxin shock' might possibly involve the release of vasoactive compounds, such as histamine, perhaps from blood neutrophils.

The clinical signs during the first 24 hours after injection in calves (F-K) may be explained by endotoxin shock. The severe, diffuse, alveolar epithelial hyperplasia in the lungs of animal (J)

was as dramatic and extensive as in the most extreme case of fog fever or complicated post-patent husk. Proliferative lesions as marked as those in calf (J) have not been experimentally induced in cattle in any published study of endotoxin shock or anaphylaxis. The reasons why this calf developed an acute respiratory distress syndrome are unknown. The pathological lesions were so extreme that they were not comparable to those of atypical interstitial pneumonia or "viral pneumonia". Animal (J) apparently developed acute respiratory distress as a result of the injection of B. pertussis suspension. The known properties of this suspension have been briefly mentioned above, amongst them are the abilities to sensitise animals to active and passive anaphylaxis and to histamine and other mediators of anaphylaxis. However, these reactions in the cow have not been associated with pulmonary lesions similar to those in calf (J). Reed et al (1972) observed that pertussis vaccine, given alone after an antigen, was capable of an anamnestic effect which resulted in the appearance of homocytotropic antibody which reacted with the antigen to which the animal had previously made a primary response. This effect was discovered in one of the five animals in the experimental group.

It may be hypothesised that one effect of the pertussis suspension on calf (J) was to stimulate a secondary antibody response to an antigen which the calf had already experienced. A further hypothesis would be that this antigen was a virus, such as para-influenza 3, or some agent to which the lung reacted with alveolar epithelial hyperplasia. The result of the pertussis treatment could then have been to stimulate the lung response in the absence of the antigen. These are only speculations and the reason why this particular proliferative change took place is unknown.

If the proliferation of alveolar cells in calf 9 was initiated by the pertussis suspension, then the period of 4 days between injection and death represents the time taken for this severe lesion to develop. This would confirm the field observation that illness of 3-4 days duration is necessary in fog fever before diffuse alveolar epithelial hyperplasia is manifested. Other animals (F,G, H and K) in the experimental group had marked lesions of 'cuffing pneumonia'; these had probably been exacerbated by the pertussis vaccine since the lymphoid cuffs appeared to be particularly hyperplastic.

CONCLUSIONS

Eyre (1972b) expressed the established view of fog fever and acute bovine pulmonary emphysema when he stated, "While much has been written about bovine emphysema, accurate means of differential diagnosis are lacking. The terms 'atypical pneumonia', 'fog fever' and 'emphysema' do not necessarily describe any precise syndrome. Bovine emphysema may be caused by one of several aetiological factors, and the clinical condition would seem to be the end result of lung 'damage' and not a disease per se. Exposure of cattle to noxious gases, dusts, fumes and fogs have been implicated in emphysema from time to time, but there is no reliable evidence".

At the beginning of this thesis, in the literature reviews, attention was drawn to the common belief that fog fever could arise in many different epidemiological circumstances and be associated with a variety of pulmonary lesions. This view had gained credence, despite the fact that fog fever had been known for over 100 years as a specific disease entity. Eyre (1972b) is only one of the many authors who have made the assumption that fog fever was a disease complex and have implied that this could be supported by a critical evaluation of the literature.

The results of the pathological investigation, presented here, and the clinical and epidemiological studies (to be published elsewhere) contradict the claim that 'accurate means of differential diagnosis are lacking' (Eyre 1972b). The "disease complex of fog fever" was found to be made up of many different diseases, which were distinguished clinically and pathologically. The main syndromes were fog fever; diffuse fibrosing alveolitis; extrinsic allergic alveolitis (farmer's lung); thrombosis of the posterior vena cava with pulmonary thrombo-embolism; reinfection husk; acute interstitial emphysema and pulmonary oedema; parasitic bronchitis

and atypical interstitial pneumonia. The term fog fever was used to describe a precise syndrome, in one class of stock.

One aim of this study was to distinguish and define the respiratory diseases of adult cattle and this has been done, in clinical and pathological terms. The aetiologies of several of these conditions are unknown, but it will be easier to make progress in establishing the causes now that the individual syndromes have been separated and characterised.

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APPENDIX 1POSTMORTEM LESIONS IN INDIVIDUAL CASES OF FOG FEVER

ANIMAL	1	AGE	A	SEX	F	BREED	Angus	DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES								LUNGS	

<p>Marked congestion and many petechial haemorrhages were in the larynx, trachea and bronchi.</p> <p>Focal haemorrhages with small quantities of free blood were found in some bronchi. A small volume of oedema fluid was present. Lymphocytes, eosinophils and some plasma cells were in the bronchial lumen and between adjacent epithelial cells. Globule leucocytes were frequent.</p> <p>Neutrophils were frequent in small bronchioles along with hyaline membrane deposits.</p> <p>Severe congestion, moderate oedema and a moderate infiltrate of plasma cells and lymphocytes were in the lamina propria.</p>	<p>Diffuse pulmonary congestion with severe pulmonary oedema (3+) and interstitial emphysema (3+).</p> <p>Many lung lobules were smooth and red-purple coloured.</p> <p>Pulmonary oedema, hyaline membranes, many large mononuclear cells, frequent eosinophils and free R.B.C.'s were found in alveolar spaces.</p> <p>Alveolar epithelial hyperplasia was mild (1+).</p> <p>Alveolar septal congestion and eosinophil infiltration were observed. Interlobular septa were dilated by oedema and gas bullae; an eosinophil and macrophage infiltration was present.</p>
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Other Findings

Congestion, petechial haemorrhages and ulceration were frequently seen in the abomasum.

ANIMAL 2 AGE A SEX F BREED Hereford DATE OF EXAMINATION September

TRACHEA, BRONCHI & BRONCHIOLES

LUNGS

Marked congestion of trachea, bronchi and larynx with very many petechial haemorrhages

Small volume of white froth in the airways.

Bronchi and bronchioles contained granular protein precipitate, hyaline membrane strands, a variable number of macrophages, a few eosinophils and neutrophils.

Sloughed epithelial cells with occasional globule leucocytes were common at higher levels.

Frequent globule leucocytes in the epithelium of the bronchial tree, where this was intact.

Lamina propria very congested and haemorrhages frequent. Oedema of lamina propria noted. Plasma cells and lymphocytes commonly found at all levels, occasionally formed into aggregates. Eosinophils often seen in such aggregates and in other parts of lamina propria.

Connective tissue around the bronchi and bronchioles oedematous and plasma cells, lymphocytes and eosinophils were frequent. Plasma cell and lymphoid aggregates found about small bronchioles.

Lungs deep red-purple in colour, severely congested.

Severe interstitial emphysema (3+) and pulmonary oedema of moderate degree (2+). Oedema and hyaline membranes apparent in most alveoli. Focal intra-alveolar haemorrhage frequent. Occasional neutrophils, moderate number of eosinophils, small number of macrophages formed a light cellular exudate in lumen. Giant cells infrequent.

Short epithelial ribbons of 4-6 cells found in many alveoli; peripheral alveoli often lined by cuboidal cells. Most alveolar septa very congested; eosinophils frequently present.

Peripheral alveolar septa often oedematous and dilated.

Interlobular septa grossly distended by gas bullae and oedema. Lymphatic channels swollen and contain occasional neutrophils, many eosinophils, macrophages and giant cells and plasma cells.

Perivascular oedema of many small pulmonary vessels, mainly veins. Some cells of media lost their staining affinity. Eosinophils sometimes seen in the intima of small veins and in their connective tissue.

Other Findings Lungs only were received. Mediastinal lymph nodes haemorrhagic, oedematous and contained large gas bullae.

Other Findings Mediastinal lymph nodes enlarged and oedematous. Long-standing Fasciola hepatica infestation of the liver. Patechial haemorrhages frequent on the epicardium and endocardium.

						DATE OF	
ANIMAL	4	AGE	A	SEX	F	BREED	Hereford
						EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
Severe congestion of trachea and bronchi.						Lungs heavy (8260gm.), very oedematous (3+) and affected by severe interstitial emphysema (3+).	
Thick, yellow mucous plugs found in lobar and segmental bronchi, especially of the apical lobes.						Many lung lobules dark red-purple, very congested and glistened on section.	
Small mucous plugs, desquamated epithelial cells, small numbers of eosinophils and neutrophils found in the bronchial and bronchiolar lumina. Basophilic hyaline deposits were seen occasionally.						Some lobules collapsed.	
Globule leucocytes frequent even though the epithelium often sloughed.						Marked pulmonary oedema, hyaline membrane formation and some intra-alveolar haemorrhage. Many large mononuclear cells, giant cells and some eosinophils in the lumen.	
Congestion, oedema and a moderate infiltration by lymphocytes, plasma cells and eosinophils in the lamina propria.						Alveolar epithelial hyperplasia (1+) present in some lobules.	
A light infiltration of the peribronchial connective tissue by lymphocytes and plasma cells.						Septal congestion often severe: oedema and eosinophil infiltration sometimes.	
						Interlobular septa oedematous, gas bullae frequent and eosinophils (sometimes in aggregates) and giant cells frequent in and around lymphatic vessels.	

Other Findings Excess (100ml.) clear pericardial fluid. Large oedematous mediastinal lymph nodes. Telangiectasis of the liver.

ANIMAL 5 AGE A SEX F BREED Hereford					DATE OF EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
<p>Marked congestion of larynx, trachea and bronchi with very many petechial haemorrhages.</p> <p>Moderate volume of white frothy fluid in the airways.</p> <p>Sloughed epithelial cells filled the lumina of many smaller bronchioles. Occasional macrophages, eosinophils and neutrophils found between desquamated cells.</p> <p>Globule leucocytes occasional in the epithelium. Lymphocytes were identified between bronchial epithelial cells still in place.</p> <p>Plasma cell and lymphocyte accumulation light in the lamina propria.</p> <p>Eosinophils found singly, often beneath the epithelium. Congestion severe and oedema apparent at many levels.</p> <p>Plasma cells and lymphocytes found in peribronchial connective tissue in small numbers.</p>					<p>Lungs deep red-purple in colour with severe congestion.</p> <p>Severe interstitial emphysema (3+) and moderate pulmonary oedema (2+) recorded.</p> <p>Alveolar oedema and hyaline membranes consistent findings.</p> <p>Cellular exudate generally sparse; large mononuclear cells predominated with smaller numbers of eosinophils and neutrophils. Occasionally exudate heavy; mainly large mononuclear cells.</p> <p>Alveolar epithelial hyperplasia (1+) confined to short rows lining some alveoli.</p> <p>Alveolar septal capillaries congested; eosinophils frequent.</p> <p>Interlobular septa dilated by gas bullae; lymphatics distended by oedema fluid in which small numbers of macrophages present. Eosinophils, lymphocytes and plasma cells found in the connective tissue in small numbers.</p> <p>Some pulmonary blood vessels affected by perivascular oedema; swelling of cells of the media, and loss of staining affinity.</p>	

Other Findings The mediastinal lymph nodes enlarged and oedematous.

A small number of Fasciola hepatica found in thickened bile ducts. Many petechial haemorrhages noted on the epicardium.

ANIMAL 6 AGE 3y SEX F BREED Galloway					DATE OF EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Deep congestion, very large number of petechial haemorrhages found in trachea and lobar bronchi.					Apical, cardiac and ventral diaphragmatic lobes deep red with congestion. The surface smooth and glistening.	
Small volume of reddish brown oedema fluid present in the lobar bronchi.					Moderate degree of pulmonary oedema (2+) and severe interstitial emphysema (3+).	
Bronchial lumen contained a small quantity of granular protein precipitate, macrophages and sloughed epithelial cells.					Many large mononuclear cells, eosinophils and neutrophils seen in the alveolar lumina. Thick, eosinophilic hyaline membranes found in most alveoli and alveolar ducts.	
Epithelial sloughing extensive - globule leucocytes could not be distinguished.					Pulmonary oedema present in most sections. Intra-alveolar haemorrhage frequent.	
Congestion, oedema and a moderate infiltration of plasma cells and lymphocytes noted in the lamina propria.					Alveolar epithelial hyperplasia not recorded.	
Small aggregates of plasma cells and lymphocytes found in the peribronchiolar connective tissue.					Alveolar septa congested; eosinophils frequent.	
					Interlobular septa dilated by oedema and gas bullae; a few eosinophils, macrophages and giant cells found in and about lymphatic vessels.	

Other Findings Many gas bullae and focal haemorrhages in the mediastinal lymph nodes. This animal also had traumatic reticulitis.

					DATE OF	
ANIMAL	7	AGE	6y	SEX	F	BREED
					Hereford	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Severe congestion, many petechial haemorrhages in larynx, trachea and bronchi.					All lung lobes deep red-purple in colour, deeply congested.	
Blood tinged frothy fluid present in moderate volume in trachea and bronchi.					Moderate pulmonary oedema (2+) and marked interstitial emphysema (3+).	
Desquamated epithelial cells; granular protein precipitate seen in larger bronchi. Smaller airways contained ghost cell outlines, free R.B.C.'s, small deposits of hyaline membrane material, occasional eosinophils.					Some alveoli overinflated, others very oedematous and collapsed. Many alveoli contained hyaline membranes, a large proportion of neutrophils, some large mononuclear cells, granular protein precipitates and free R.B.C.'s; in this latter group there was alveolar epithelial hyperplasia.	
Desquamated epithelial cells common. Globule leucocytes not distinguished.					Alveolar epithelial hyperplasia (1+) frequent in some lobules.	
Light plasma cell and lymphocyte infiltration of the lamina propria, sometimes increased to form small aggregates. Congestion and oedema common findings.					Alveolar septal congestion severe; septal oedema present.	
Peribronchial connective tissue contained small numbers of plasma cells and lymphocytes.					Gas bullae frequent in interlobular septa. Oedematous connective tissue often contained many plasma cells, lymphocytes and eosinophils.	
					Perivascular oedema and medial swelling of small vessels frequent.	

Other Findings Oedema of connective tissue of mediastinum. Enlarged oedematous mediastinal lymph nodes. Lungs only received.

ANIMAL 8	AGE A	SEX F	BREED Hereford	DATE OF EXAMINATION	November
TRACHEA, BRONCHI & BRONCHIOLES				LUNGS	

<p>Severe congestion of larynx, trachea and bronchi.</p> <p>Abundant white frothy fluid in airways.</p> <p>Small volume of granular protein precipitate and macrophages seen in the bronchial lumen.</p> <p>Globule leucocytes frequent.</p> <p>Oedema and congestion of the lamina propria with a moderate plasma cell and lymphocyte infiltration.</p> <p>Plasma cell and lymphocyte infiltration sometimes heavy in the peribronchial connective tissue.</p>	<p>Apical, cardiac and ventral diaphragmatic lobes dark red-purple in colour and rubbery in consistency.</p> <p>Severe interstitial emphysema (3+) and moderate (2+) pulmonary oedema.</p> <p>Granular protein deposits, hyaline membranes and many large mononuclear cells found in the alveolar lumen.</p> <p>Eosinophils and neutrophils frequent.</p> <p>Alveolar epithelial hyperplasia frequent (2+).</p> <p>Alveolar septal congestion pronounced, oedema frequent and light infiltration of eosinophils.</p> <p>Interlobular septa dilated by oedema and gas bullae; moderate infiltrate of lymphocytes and plasma cells with a smaller number of eosinophils.</p> <p>Perivascular oedema and cuffing by lymphocytes and plasma cells frequent.</p> <p>Medial swelling in some small venules.</p>
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Other Findings Lungs only received for examination. The mediastinal lymph nodes enlarged and contained many gas bullae associated with focal haemorrhages.

					DATE OF	
ANIMAL	9	AGE	A	SEX	F	BREED
						Blue/Grey
					EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Severe congestion and a large number of petechial haemorrhages found in larynx, trachea and bronchi. Abundant white frothy fluid in trachea and bronchi. Desquamated epithelial cells with some macrophages, neutrophils and eosinophils found in lumen. Globule leucocytes frequent in the tracheal epithelium. Oedema, congestion and light plasma cell and lymphocyte infiltration of lamina propria of bronchi and bronchioles. Eosinophils present in small numbers. Peribronchial infiltration and accumulation of plasma cells and lymphocytes; especially in apical lobes.					Lungs deep red-purple in colour and very congested, particularly antero-ventrally. Severe interstitial emphysema (3+) and moderate pulmonary oedema. Many alveoli overinflated, alveolar ducts and bronchioles contained hyaline deposits, macrophages and a few neutrophils. Other alveoli oedematous with hyaline membranes (1+) and proliferation of alveolar epithelial cells (1+). Alveolar spaces empty or contained alveolar macrophages, a few neutrophils. Basophilic deposits infrequent. Alveolar septa oedematous, congested and contained eosinophils, neutrophils and large mononuclear cells. Interlobular septa dilated by gas and oedema. Macrophages, plasma cells, lymphocytes and multinucleated giant cells in and around lymphatic vessels. Perivascular oedema and gas; loss of staining affinity of media of venules.	

Other Findings Mediastinal lymph nodes enlarged and oedematous; haemorrhages and gas bullae frequent. Many petechiae on endocardium and epicardium. Mild bile duct fibrosis and calcification.

						DATE OF	
ANIMAL	10	AGE	8y	SEX	F	BREED	Galloway
						EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
Very severe congestion of larynx, trachea and bronchi with many petechial and focal haemorrhages leading to small amounts of frank blood in the trachea and lobar bronchi.						Apical, cardiac and ventral diaphragmatic lobes deep purple in colour, firm and rubbery on palpation. Severe interstitial emphysema (3+) and mild pulmonary oedema (1+).	
Histological specimens poor due to postmortem change. Many sloughed epithelial cells filled the bronchial lumen. In bronchioles, neutrophils, macrophages and granular protein precipitates were found.						Many fibrous pleural tags noted on the right diaphragmatic lobe surface. Lungs weighed 9kgm.	
No globule leucocytes found in sloughing epithelium.						Many alveoli overdistended but otherwise normal. Others filled by oedema fluid, hyaline membranes and macrophages. Neutrophils and eosinophils infrequent.	
Oedema and congestion of the lamina propria common.						Alveolar epithelial hyperplasia absent. Alveolar septa congested.	
Light plasma cell and lymphocyte infiltration of propria and peribronchial connective tissue, present.						Interlobular septa dilated by oedema and gas bullae. Lymphocytes, plasma cells and eosinophil infiltration light. Perivascular oedema and medial swelling present.	

Other Findings The mediastinal lymph nodes enlarged, oedematous and contained many small gas bullae associated with focal haemorrhages.

ANIMAL 11 AGE 5y SEX F BREED Hereford					DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	

Small volume of white froth and thick green mucous plugs present in trachea and bronchi.

Marked congestion and many petechial haemorrhages recorded in the larynx, trachea and bronchi.

Many desquamated epithelial cells, granular protein precipitate and some macrophages found in lumen of bronchi and bronchioles.

Most of the epithelium sloughed; globule leucocytes not identified.

Lamina propria congestion and oedema marked. Plasma cells, lymphocytes and eosinophils frequent.

Plasma cells and lymphocytes consistently found around bronchi and bronchioles often in small aggregates.

Apical, cardiac and diaphragmatic lobes deep red-purple in colour and rubbery in texture.

Moderate pulmonary oedema (2+) and severe (3+) interstitial emphysema.

Hyaline membrane deposits, precipitated protein, frequent alveolar macrophages and small numbers of eosinophils and neutrophils found in the lumen.

Short ribbons of 2-5 cells found in small proportion of alveoli.

Alveolar capillaries congested.

Many gas bullae in the interlobular septa. Lymphatics dilated and contained a small number of eosinophils, macrophages, lymphocytes and plasma cells.

Perivascular oedema and some loss of staining affinity of small vessels seen.

Other Findings The mediastinal lymph nodes enlarged and oedematous.

Petechial haemorrhages frequent on the epicardium; a large haemorrhage found in the perivascular connective tissue about the proximal 30cm. of the aorta.

ANIMAL 12 AGE A SEX F BREED Hereford					DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Large haemorrhage in fascia dorsal to larynx.					Apical, cardiac and diaphragmatic lobes deep red-purple in colour and rubbery in consistency.	
Marked congestion and many petechial haemorrhages in larynx, trachea and bronchi.					Severe interstitial emphysema (3+) and moderate pulmonary oedema (2+).	
Small volume white frothy fluid in trachea and larynx, less fluid in bronchi.					Lobules in the diaphragmatic lobes fawn-brown in colour, less congested.	
Granular protein precipitate found in lumen of larger bronchi. Small bronchioles contained many					Hyaline membrane deposits, precipitated protein granules and focal haemorrhage frequently seen in alveoli.	
sloughed epithelial cells, with giant cells and neutrophils inter-mixed. Haemorrhage in smaller bronchioles.					Cellular exudation was moderate - mainly large mononuclear cells, macrophages and neutrophils with smaller numbers of eosinophils and giant cells.	
Epithelium of most bronchioles sloughed and cytology poor.					Alveolar epithelial hyperplasia confined to occasional rows of 3-10 cells in some alveoli.	
Eosinophils in small numbers and many plasma cells and lymphocytes present in the lamina propria.					Alveolar septa very congested; neutrophils and eosinophils observed in the capillaries.	
Severe congestion and moderate oedema noted.					Interlobular septa oedematous, many gas bullae apparent. Cellular infiltration moderate - many eosinophils, lymphocytes and plasma cells in the connective tissue and frequent eosinophils, neutrophils, lymphocytes and giant cells in the lymphatic vessels. Focal lymphoid aggregates present also.	
Plasma cells and lymphocytes found in the peribronchial connective tissue at all levels, sometimes arranged in aggregates.					Perivascular oedema and medial swelling common - medial cells lost their staining affinity of venules.	

Other Findings Large haemorrhages in the perivascular connective tissue of the proximal aorta and right pulmonary vein. Petechial haemorrhages frequent on the epicardium and endocardium. Many 1-2cm. diameter crateriform ulcers were found on the abomasal folds.

ANIMAL 13 AGE A SEX F BREED Hereford					DATE OF EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Severe congestion of larynx, trachea, bronchi, with many petechial haemorrhages.					Apical and cardiac lobes dark red, congested and rubbery in consistency.	
Very small volume whitish frothy fluid in bronchi, trachea.					Severe interstitial emphysema (3+) and moderate pulmonary oedema (2+) found in diaphragmatic lobes, many lobules deep purple in colour and very heavy. Small number of fibrous tags present on the caudal diaphragmatic lobe pleura.	
Very many sloughed epithelial cells filled small bronchioles.					Majority of acini filled by granular protein deposits and hyaline membranes.	
Small numbers of macrophages, occasional neutrophils and granular protein deposits also.					A variable number (generally small but focally high) of alveolar macrophages phagocytosing this material. Intra-alveolar haemorrhage common and sometimes intense. Neutrophils and giant cells also found.	
Hyaline membrane deposits, infiltrated by neutrophils, in some small bronchioles.					Alveolar epithelial hyperplasia confined to rows of 6-10 cells on, or just separated from, the alveolar septa in some alveoli.	
Little epithelium remained on the larger bronchi but where this was intact an occasional intra-epithelial globule leucocyte could be distinguished.					Alveolar septa very congested, small numbers of eosinophils present.	
Small numbers of intra-epithelial lymphocytes also noted.					Interlobular septa very oedematous, frequent gas bullae found. Cellular infiltrate generally a small number of plasma cells and lymphocytes but neutrophils predominated in some lobules.	
Severe lamina propria congestion and haemorrhage in lobar bronchi.					Perivascular oedema; focal loss of staining affinity in media of small pulmonary venules.	
Light infiltration of plasma cells and lymphocytes, sometimes formed into small sub-epithelial aggregates.						
Small numbers of plasma cells and lymphocytes found in the connective tissue about bronchi and bronchioles.						

Other Findings Mediastinal lymph nodes were enlarged and oedematous and several small gas bullae were present. A long standing Fasciola hepatica infestation was found in the liver.

						DATE OF	
ANIMAL	14	AGE	4y	SEX	F	BREED	Hereford
						EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
<p>Severe congestion, large number of petechial haemorrhages found in larynx, trachea and bronchi. Abundant white, frothy fluid ran from trachea and was in the lobar bronchi.</p> <p>Desquamated epithelial cells, granular protein precipitate and some portions of hyaline membrane found in many smaller bronchi and bronchioles. Small numbers of macrophages, neutrophils, eosinophils and an occasional globule leucocyte present amongst the luminal debris. Small mucous plugs noted in a minority of bronchioles. Desquamation of the epithelium common but frequent globular leucocytes could be seen in between and below the separating epithelial cells. Lymphocytes seen between adjacent epithelial cells in some places.</p> <p>Congested oedematous lamina propria infiltrated by a varying number of plasma cells and lymphocytes with small numbers of eosinophils.</p> <p>Plasma cells and lymphocyte infiltration heavy in apical lobes.</p> <p>Peribronchial infiltration and accumulation of plasma cells and lymphocytes particularly heavy in apical lobes where infiltration extended into interlobular septa.</p>						<p>Lungs deep red-purple in colour, deeply congested over the apical lobes.</p> <p>Severe pulmonary oedema (3+) and interstitial emphysema (3+).</p> <p>Many alveoli overdistended and associated alveolar ducts blocked by hyaline membrane deposits. Other alveoli contained granular protein precipitate, heavy hyaline membrane deposits, a moderate number of alveolar macrophages, small numbers of neutrophils and some eosinophils.</p> <p>Basophilic hyaline membranes occasionally seen. Giant cells common.</p> <p>Epithelial hyperplasia striking in some lobules but others had no sign of hypercellularity. Graded (2+).</p> <p>Alveolar septa oedematous and congested. Small numbers of plasma cells and lymphocytes seen in dilated septa along with more frequent eosinophils and neutrophils. Eosinophils arranged in aggregates of 20-40 cells in places.</p> <p>Interlobular septa dilated by oedema and gas bullae. Lymphatic vessels contained many macrophages and giant cells; eosinophils frequently found in and around these vessels.</p> <p>Oedematous connective tissue often contained many plasma cells, lymphocytes and eosinophils, in aggregates at septal junctions. Perivascular oedema, loss of staining affinity of venules. Eosinophils often seen in the lumen, walls and adventitia of such vessels.</p>	

					DATE OF				
ANIMAL	15	AGE	5y	SEX	F	BREED	Hereford	EXAMINATION	October (found dead)

TRACHEA, BRONCHI & BRONCHIOLES

LUNGS

Severe congestion and many petechial haemorrhages in the larynx and trachea.

Large volume of white frothy fluid found at the nose, but little in trachea or bronchi.

Lumen of large bronchi empty; many desquamated epithelial

cells, some hyaline membrane deposits (eosinophilic and basophilic). Small numbers of

neutrophils, macrophages and eosinophils, ghost cell outlines and granular protein

precipitates in smaller bronchioles. Extensive epithelial

desquamation, but globule leucocytes still discernible. Oedema congestion and light

plasma cell and lymphocyte infiltration frequent in the lamina propria.

Small numbers of neutrophils and some eosinophils also found especially in the apical lobes.

Light peribronchial plasma cell and lymphocyte infiltration observed, occasionally in the

form of larger aggregates. Small aggregate of lymphocytes with some plasma cells found

adjacent to a terminal bronchus near the interlobular septum in one section. No eosinophilic/ granular centre.

Apical, cardiac and ventral diaphragmatic lobes dark red, rubbery and very congested.

Severe interstitial emphysema (3+) and moderate (2+) pulmonary oedema recorded.

In most lobules, many mononuclear cells, basophilic and eosinophilic hyaline membranes, giant cells and R.B.C.'s found to fill the alveolar lumen. Some lumina normal but overinflated, others contained many neutrophils, especially in the apical lobes. Pulmonary oedema in lobules not overinflated.

Alveolar epithelial hyperplasia extensive, though not present in some portions of apical and diaphragmatic lobes. Graded (2+)

Most alveolar septa congested, some oedematous and the thickened parts contained mononuclear cells, neutrophils and eosinophils.

Interlobular septa oedematous and some gas bullae noted. Many neutrophils and eosinophils present. An infiltrate of plasma cells and lymphocytes was sometimes heavy.

Perivascular oedema with medial swelling of small pulmonary vessels noted. Light cuffing of vessels by plasma cells and lymphocytes.

Other Findings Large gas bullae and many focal haemorrhages were found in enlarged oedematous mediastinal lymph nodes. Focal haemorrhages found in the connective tissue around the proximal aorta and pulmonary artery.

ANIMAL 16 AGE 8y SEX F BREED Shorthorn						DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
Marked congestion and many petechial haemorrhages in the trachea and lobar bronchi.						Right apical and cardiac lobes dark red, and had a few foci of interstitial emphysema and oedema.	
Thick, yellow mucous strands in some lobar and segmental bronchi.						Left apical and cardiac lobes congested and moderate pulmonary oedema (2+) and interstitial emphysema (2+) recorded.	
Small volume of white froth in airways.						Diaphragmatic lobes dark purple in colour, moderately oedematous (2+) and severely affected by interstitial emphysema (3+).	
Extensive epithelial desquamation and many cells found in the bronchial lumina. Small hyaline membrane deposits, granular protein precipitates, free R.B.C.'s also.						The lumen of many alveoli contained fine hyaline membranes, granular protein deposits, an increased number of mononuclear cells and free R.B.C.'s.	
Mucous plugs filled some small bronchioles.						Neutrophils numerous in some sections.	
Globule leucocytes frequent intra-epithelially, where this was intact, or amongst desquamated cells.						Alveolar epithelial hyperplasia confined to a focal hypercellularity of some acini.	
Lamina propria congestion and oedema was frequent. Plasma cell and lymphocyte infiltration sometimes heavy.						Alveolar septa very congested and neutrophils and eosinophils could be seen in the vessels.	
Peribronchial lymphocyte and plasma cell infiltration light.						Interlobular septa oedematous and aggregates of plasma cells, lymphocytes with some neutrophils seen. Eosinophils sparse. Gas bullae present.	
						Perivascular oedema and occasional vascular lesions (medial swelling) found.	

Other Findings 100ml. clear pericardial fluid was found. A longstanding Fasciola hepatica infestation of the liver was present. The mediastinal lymph nodes were enlarged, oedematous and contained small gas bullae.

					DATE OF	
ANIMAL	17	AGE	A	SEX	F	BREED
					Hereford	EXAMINATION
					November	
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Very severe congestion of larynx, trachea and bronchi, with a very large number of petechial haemorrhages in all parts.					Apical, cardiac and ventral diaphragmatic lobes deep purple in colour, very congested and rubbery in texture.	
Abundant reddish brown oedema fluid in all bronchi and trachea.					Severe interstitial emphysema (3+) and moderate pulmonary oedema (2+) recorded.	
Many sloughed epithelial cells filled the lumen of bronchi and bronchioles. Hyaline membrane material, granular protein precipitate and many neutrophils also found.					Pulmonary oedema and hyaline membrane deposits, focal haemorrhage, many macrophages, eosinophils and neutrophils in alveolar lumina. Some very overinflated. Alveolar epithelial hyperplasia seen in some alveoli (1+).	
No globule leucocytes seen - there was severe epithelial sloughing.					Severe septal congestion with a light eosinophil infiltration noted.	
Heavy plasma cell and lymphocyte infiltration of the lamina propria.					Interlobular septa oedematous and gas bullae frequent. Fibrin plugs, giant cells and eosinophils present in lymphatics. Plasma cell and lymphocyte infiltration moderate.	
Congestion and oedema present.					Perivascular oedema extensive, medial swelling frequent.	
Plasma cell and lymphocyte infiltration of the peribronchial connective tissue heavy.						

Other Findings Only the lungs were received for examination. The mediastinal lymph nodes were enlarged, oedematous and contained many gas bullae associated with focal haemorrhages.

					DATE OF	
ANIMAL	18	AGE	A	SEX	F	BREED
					Hereford	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Deep congestion of trachea and bronchi with occasional petechial haemorrhages.					Apical and cardiac lobes deep red-purple and rubbery on palpation.	
Thin, whitish mucous plugs in the lumen of many lobar bronchi.					Diaphragmatic lobes overexpanded generally and severe interstitial emphysema (3+) and moderate pulmonary oedema (2+) recorded.	
Desquamated epithelial cells and granular protein precipitate seen in bronchial lumina. Free R.B.C.'s and clumps of basophilic hyaline membrane in bronchioles.					The right lung weighed 5580gm; the left 3180gm.	
Globule leucocytes frequent.					Most alveoli from diaphragmatic lobes overinflated. Apical and cardiac lobe alveoli often contained hyaline membranes,	
Oedema, congestion and light plasma cell and lymphocyte infiltration seen in the lamina propria.					neutrophils, eosinophils, macrophages and R.B.C.'s. Alveolar epithelial hyperplasia was well developed in apical and cardiac lobes (2+).	
Light peribronchial infiltration of lymphocytes and plasma cells noted.					Alveolar septa congested and often oedematous with increased numbers of mononuclear cells, eosinophils and neutrophils infiltrating.	
					Oedema, gas bullae and fibrin clots frequent in interlobular septa.	
					Lymphocyte and plasma cell aggregates and eosinophils common.	
					Perivascular oedema and medial swelling in small vessels noted.	

Other Findings The mediastinal lymph nodes were enlarged and oedematous. Many petechial haemorrhages observed in the wall of the abomasum and a 45cm. long portion of mid-ileum. Blood tinged, brownish watery fluid containing leaves, twigs and small stones was found in the abomasum and the affected portion of intestine.

DATE OF									
ANIMAL	19	AGE	3y	SEX	F	BREED	Hereford	EXAMINATION	November
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS			
Most small bronchioles contained many desquamated cells and macrophages with small numbers of giant cells and neutrophils. Bronchial and bronchiolar epithelium generally sloughed; globule leucocytes could not be distinguished.						Fixed portions of lung received in 10% formalin; severe interstitial emphysema and oedema noted.			
Severe congestion and oedema of the lamina propria with a light infiltration of plasma cells and lymphocytes, occasionally these had formed into aggregates.						Many mononuclear cells filled the alveolar lumina. Hyaline deposits, granular protein precipitate, many neutrophils and giant cells also found. Eosinophils sparse.			
Neutrophils often frequently found in the lamina propria.						Alveolar epithelium hyperplastic and most alveoli lined by cuboidal cells, though many appeared desquamated (3+).			
Heavy plasma cell and lymphocyte infiltration around the bronchi and bronchioles.						Alveolar septal congestion severe and oedema notable.			
						Many gas bullae dilated the interlobular septa. The lymphatics dilated and contained many plasma cells, lymphocytes, giant cells and neutrophils.			
						Perivascular cuffing by lymphocytes and plasma cells, perivascular oedema and swelling of medial cells observed.			

					DATE OF	
ANIMAL	20	AGE	3y	SEX	F	BREED
						Hereford
					EXAMINATION	November
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
<p>Most bronchial lumena empty or contained desquamated epithelial cells. This was also found in the bronchioles, though one contained a large plug of basophilic hyaline deposit which was infiltrated by neutrophils and macrophages. Small numbers of neutrophils and macrophages found without small hyaline strands also.</p> <p>Globule leucocytes could be distinguished in parts where epithelial sloughing was not total. Oedema, severe congestion, a light plasma cell infiltration and small numbers of eosinophils and lymphocytes were all noted in the lamina propria.</p> <p>Light plasma cell and lymphocyte infiltration present in the peribronchial connective tissue.</p>					<p>Fixed portions of lung received in 10% formalin. Severe interstitial emphysema in the portions examined and extensive interstitial oedema.</p> <p>Hyaline membranes, granular protein precipitate, free R.B.C.'s and variable numbers of alveolar macrophages found in most alveolar lumena with a small proportion of neutrophils and eosinophils.</p> <p>Alveolar epithelial hyperplasia common (2+).</p> <p>Alveolar septa congested and eosinophils and neutrophils were present. Many large gas bullae and oedematous connective tissue observed in interlobular septa. Cell infiltration light. Perivascular oedema and loss of medial staining affinity seen in small pulmonary vessels.</p>	

ANIMAL 21 AGE 7y SEX F BREED Blue/Grey DATE OF EXAMINATION November

TRACHEA, BRONCHI & BRONCHIOLES

LUNGS

Many petechial haemorrhages present in larynx, trachea and bronchi. Much reddish brown oedema fluid noted in right bronchial system; thick green yellow mucous plugs occasionally seen in the left side; no oedema. Lumen of many bronchi and bronchioles contained sloughed epithelial cells, globule leucocytes, neutrophils, hyaline membrane deposits and R.B.C.'s. Most of the epithelium of bronchi and bronchioles was sloughed but frequent globule leucocytes noted in more intact portions. Congestion was severe in the lamina propria vessels. Oedema, light plasma cell and lymphocyte infiltration present. Eosinophils common. Plasma cells and lymphocytes found in small numbers in the peribronchial connective tissue.

Right lung severe congestion, moderate pulmonary oedema (2+) and severe interstitial emphysema (3+). Most lung lobules dark red-purple in colour. Left lung most lobules fawn-brown in colour, less congestion and oedema, severe interstitial emphysema (3+). Small number of fibrous pleural tags seen on the diaphragmatic lobe surface. The alveolar lumen in many acini filled by hyaline membranes, granular protein deposits, many alveolar macrophages and smaller proportions of neutrophils, eosinophils and giant cells. Some acini collapsed, others were overinflated. Alveolar epithelial hyperplasia confined to peripheral acini of some lobules; not a prominent feature (1+). Alveolar septal congestion marked in the right lung. Septal oedema occasionally recorded. Gas bullae distended many interlobular septa. Engorged lymphatics contained a mix cell population of macrophages, lymphocytes, neutrophils and eosinophils. Perivascular oedema and medial swelling seen in small pulmonary vessels.

Other Findings Longstanding Fasciola hepatica infestation of the liver. Calcification of the intima of proximal aorta and left atrium.

ANIMAL 22 AGE A SEX F BREED Galloway						DATE OF EXAMINATION	November
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
Moderate number of petechial haemorrhages found in the trachea, which was mildly congested.						Apical, cardiac and ventral diaphragmatic lobes deep red-purple in colour and rubbery in consistency.	
Small volume of white frothy fluid present in upper airways.						Severe interstitial emphysema (3+) and moderate pulmonary oedema (2+) also recorded.	
Lobar bronchi often contained small quantities of granular protein precipitate and macrophages. Small bronchioles filled by granular protein precipitate, hyaline membrane deposits and a cellular exudate of macrophages, neutrophils and occasional eosinophils.						Large, sub-pleural gas bullae notable.	
Globule leucocytes frequent in the bronchial epithelium.						The right lung weighed 3690gm; the left 2100gm.	
Consistent heavy infiltration of plasma cells and lymphocytes present in the lamina propria.						Thick hyaline membranes, granular protein deposits, many macrophages and frequent neutrophils with occasional focal haemorrhages found in most alveoli.	
Congestion and oedema noted also.						Eosinophils frequent in the lumen.	
Plasma cells and lymphocytes often arranged in small aggregates in the peribronchial connective tissue.						Alveolar epithelial hyperplasia extensive in most alveoli (2+).	
						Alveolar septal congestion and oedema widespread. Neutrophils and frequent eosinophils infiltrated the septum.	
						Gas bullae and oedema dilated the interlobular septa. Plasma cells and lymphocytes consistently seen; eosinophils and macrophages also found.	
						Perivascular oedema and medial swelling of small vessels seen.	

Other Findings The mediastinal lymph nodes were enlarged and oedematous.

ANIMAL 23 AGE 3y SEX F BREED Hereford					DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
<p>Marked congestion and many petechial haemorrhages present in the larynx, trachea and lobar bronchi.</p> <p>Small volume of white frothy fluid found in the trachea and lobar bronchi.</p> <p>Sloughing of epithelium of most of lobar and smaller bronchi, with plugs of desquamated cells filling the lumina, had occurred. Globule leucocytes are also found in amongst these cells, infrequently. Hyaline membranes present in smaller bronchioles; such membranes often very basophilic.</p> <p>The lamina propria of the bronchial tree was congested and in many places oedematous. A moderate number of plasma cells and lymphocytes also present.</p> <p>Aggregates of plasma cells and lymphocytes found in the peri-bronchiolar connective tissue.</p>					<p>The lungs were oedematous (2+) and many apical, cardiac and ventral diaphragmatic lobules dark red in colour. The cut surface of the lung revealed many smooth, glistening, red lobules and severe interstitial emphysema (3+).</p> <p>Pulmonary oedema present in most lobules and thick hyaline membranes lined most alveoli and alveolar ducts. Many mononuclear cells present in alveolar lumina and many of these contained phagocytosed neutrophils, hyaline membrane material or R.B.C.'s.</p> <p>Neutrophils frequent and predominated in some alveoli. Some alveolar haemorrhage.</p> <p>Giant cells frequently present in and around hyaline membranes.</p> <p>Eosinophils present in moderate numbers in alveolar lumina.</p> <p>Widespread epithelial hyperplasia and most alveoli lined by cuboidal cells, (3+); mitotic figures occasionally seen. Alveolar septa dilated by oedema, congestion and increased numbers of large mononuclear cells and eosinophils.</p> <p>The lymphatics of the interlobular septa were dilated and many macrophages and smaller numbers of eosinophils present.</p> <p>Gas bullae dilated many lymphatics.</p>	
<u>Other Findings</u>					None on gross examination.	

ANIMAL 24 AGE 5y SEX F BREED Galloway					DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Small volume of thick, grey-green mucus in the upper trachea.					Apical, cardiac and ventral diaphragmatic lobes fawn-brown in colour and very rubbery in consistency.	
Small volume of white, frothy fluid in smaller, segmental bronchi.					Little pulmonary oedema (1+) present.	
Granular protein precipitate and a small number of eosinophils and neutrophils found in the bronchial lumen. Plugs of sometimes basophilic hyaline membranes filled small bronchioles and increased numbers of cells, both neutrophils and eosinophils were infiltrating these deposits or were found without hyaline material.					Moderate interstitial emphysema found in the diaphragmatic lobes (2+). A small number of fibrous tags present on the pleural surface of the diaphragmatic lobes.	
Many globule leucocytes found intra-epithelially and sub-epithelially in bronchi and bronchioles. Eosinophils frequent in these positions.					Hyaline membranes and giant cells frequently present, though oedema and haemorrhage were uncommon. Small numbers of mononuclear cells consistently present and these increased to form small aggregates of 5-20 cells in acini lined by cuboidal epithelium. Eosinophils and neutrophils present in small numbers.	
The lamina propria slightly oedematous and congested in the lobar bronchi.					Alveolar epithelial hyperplasia (3+) found in the majority of lung acini examined. Alveolar septa congested and dilated by oedema. Increased numbers of mononuclear cells, neutrophils and eosinophils could be distinguished in the dilated portions.	
Eosinophils, plasma cells and lymphocytes found frequently, and occasional sub-epithelial lymphoid aggregates noted.					The interlobular septa slightly dilated and the slightly enlarged lymphatic vessels contained many giant cells, eosinophils, macrophages and occasional neutrophils. Focal accumulation of eosinophils and neutrophils noted.	
Plasma cells and lymphocytes frequently seen in a peribronchiolar position. The infiltration sometimes heavy.					Gas bullae also present. Subendothelial oedema observed in many small pulmonary vessels. 2 small lymphoid nodules with germinal centres seen at the periphery of two lobules, adjacent to interlobular septa.	

Other Findings Many petechial haemorrhages were found on the epicardium.

A longstanding Fasciola hepatica infestation was noted in the liver.

					DATE OF	
ANIMAL	25	AGE	5	SEX	F	BREED
Hereford					EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
No significant findings.					Mild interstitial emphysema (1+) with	
Most bronchi and bronchioles empty.					overexpansion of dorsal, apical and	
In bronchioles supplying oedematous					cardiac lobes recorded.	
alveoli there was also oedema fluid.					The posterior half of the diaphragmatic	
Globule leucocytes common in the					lobes was deep red, congested and	
bronchial epithelium. Eosinophils					mildly oedematous (1+).	
common in epithelium, lamina					This appearance was the result of	
propria and peribronchial connective					pulmonary oedema and hyaline membranes.	
tissue of oedematous lobules.					A moderate number of eosinophils found	
					in the alveolar and interlobular	
					connective tissue. Most alveoli contained	
					only a few neutrophils or macrophages in	
					the oedema fluid.	

There was no alveolar epithelial hyperplasia.

Other Findings A small number of Ostertagia nodules and adults were found in the abomasum. The mediastinal lymph nodes were enlarged.

ANIMAL 26 AGE 5y SEX F BREED Galloway					DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
No significant gross lesions.					Severe interstitial emphysema (3+).	
Most bronchi and bronchioles were empty; a few contained neutrophils, condensed hyaline deposits and macrophages. Basophilic hyaline material was noted in terminal bronchioles.					Apical, cardiac and ventral diaphragmatic lobes fawn coloured, heavy and rubbery; collapsed lobules adjacent to gas bullae. Scattered lobules red and depressed. Many fibrous tags on caudal diaphragmatic lobes. Widespread alveolar epithelial hyperplasia in most acini of all lobes. Desquamated epithelial cells and macrophages filled the alveoli; giant cells, neutrophils and hyaline deposits frequent.	
Globule leucocytes were very numerous in the bronchial epithelium. Neutrophils were commonly found between epithelial cells.					Some acini oedematous and contained hyaline membranes.	
There was moderate lymphoid and plasma cell infiltration of the lamina propria and perivascular connective tissue. Eosinophils were sometimes found in these sites also.					Most alveoli lined by a single layer of cuboidal cells, in which mitosis was frequent.	
Some bronchioles were dilated where the muscle layer was reduced.					Alveolar septa dilated by oedema and increased numbers of interstitial cells and neutrophils. Fine collagen strands sometimes found, but no increase in reticulin. Interlobular septa contained gas bullae. Many plasma cells and lymphocytes in the lymphatics with a moderate proportion of eosinophils. Plasma cells and lymphocytes found in perivascular connective tissue along with small numbers of eosinophils.	

Other Findings A small number of adult Fasciola were found in the liver. The mediastinal lymph nodes were hyperplastic.

				DATE OF	
ANIMAL	27	AGE	2-3y	SEX	F
BREED	Hereford				
				EXAMINATION	September
TRACHEA, BRONCHET & BRONCHIOLES				LUNGS	

Small volume of white froth was confined to the lobar bronchi but the airways otherwise empty. Globule leucocytes commonly found in the bronchial epithelium but few other intra-epithelial cells. Mild oedema of the lamina propria. A moderate degree of infiltration by plasma cells and lymphocytes with a few neutrophils noted also. Eosino phils more numerous in the peribronchial connective tissue and a constant light infiltration of plasma cells and lymphocytes.

All the lobes except the dorsal part of the diaphragmatics fawn-brown in colour and fleshy in texture. Moderate interstitial emphysema (2+) present also. Most lobules examined affected by extensive alveolar epithelial hyperplasia. The alveolar spaces filled with desquamated cells, macrophages, a few neutrophils and hyaline deposits. Mitotic activity common in the alveolar epithelium and occasionally cells were double layered. Focal oedema in some lobules. Alveolar septa thickened by oedema and an increased number of interstitial cells, neutrophils and a few eosinophils.

Fibrosis light focally. Interlobular septa contained gas bullae, plasma cells, lymphocytes, macrophages and a few eosinophils.

Other Findings Mediastinal lymph nodes were enlarged and there was oedema of the mediastinal connective tissue. There was a light Fasciola burden in the liver. A small number of irregular ulcers were present on the abomasal folds. A large haemorrhage was noted at the base of the pulmonary artery.

					DATE OF	
ANIMAL	28	AGE	6	SEX	F	BREED
					EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	

No significant findings in the trachea and bronchi.

Histologically there is a little mucus containing macrophages in some bronchi.

Globule leucocytes were frequent in the bronchial epithelium but other intra-epithelial cells were few.

Lymphoid infiltration of the lamina propria and peribronchial connective tissue was light.

The lungs were pale and overinflated.

Several small grey spots 0.5mm. in diameter recorded in all lobes.

Honey-combing of the left diaphragmatic lobe tip.

Small grey spots appeared to be areas of alveolar epithelial hyperplasia involving a few acini.

In such foci, alveolar septal fibrosis was minimal and there was no lymphoid or plasma cell infiltration.

Affected acini contained neutrophils, desquamated epithelial cells and macrophages.

The lesions were very small.

The vast majority of acini in all lobes were normal.

Other Findings Light Fasciola and Ostertagia adult burdens were noted. The liver was lightly fibrosed in all lobes.

					DATE OF	
ANIMAL	29	AGE	A	SEX	F	BREED
						Hereford
					EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	

No significant findings on gross inspection.	Apical, cardiac and almost all the diaphragmatic lobes fawn-brown in colour and very fleshy.
The right lung weighed 4600gm	Moderate degree of interstitial emphysema (2+) and mild oedema (1+) recorded.
" left " " 3600gm	Large haemorrhages found in the
Total 8200gm	connective tissue at the base of the heart, in and around the wall of the pulmonary veins near the heart.
The bronchi and larger bronchioles empty but a little fluid mixed with macrophages and a few neutrophils, found in terminal bronchioles. Hyaline deposits also found.	Some lobules normal but the vast majority affected by marked alveolar epithelial hyperplasia. Alveolar spaces filled by desquamated cells, macrophages and condensed hyaline deposits.
Globule leucocytes frequent in the bronchial epithelium.	Focal oedema and neutrophils found in small numbers in the lumen and alveolar septum. Alveolar septa dilated by oedema and there was an increase in the number of interstitial cells.
Plasma cells and lymphocytes with some neutrophils and a few eosinophils found in the lamina propria and peribronchial connective tissue.	Interlobular septa slightly oedematous and contained gas bullae.

Other Findings There were many ulcers on the abomasal folds. A mild Fasciola burden in the liver and enlargement of the mediastinal lymph nodes also noted. Sarcocysts were noted frequently in heart muscle.

ANIMAL 30 AGE A SEX F BREED Hereford					DATE OF EXAMINATION September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS
<p>Small volume of whitish frothy fluid present in the trachea and bronchi. A few macrophages and neutrophils with a little oedema or hyaline material noted in many small bronchioles in areas of alveolar epithelial hyperplasia. Globule leucocytes were abundant in the bronchial epithelium. Migrating neutrophils and a few eosinophils also found. The lamina propria occasionally oedematous. A moderate plasma cell and lymphocyte infiltration sometimes formed into aggregates or augmented focally by neutrophils or eosinophils. Plasma cells and lymphocytes surrounded many bronchi and bronchioles. A focus of bronchiolitis obliterans in the apical lobe was associated with an area of alveolar overinflation.</p>					<p>Right apical and both cardiac lobes congested, red-brown in colour, fleshy in texture with smooth, glistening cut surface. Pulmonary oedema (1+) confined to these lobes and severe interstitial emphysema (3+) noted in the diaphragmatic lobes. Many collapsed lobules observed around larger gas bullae. Histologically, lobules either over-inflated and affected by interstitial emphysema or alveolar epithelial hyperplasia present (in some cases the lobules were collapsed). Emphysematous lobules sometimes contained oedema fluid and fine hyaline membranes. Cuboidal epithelial hyperplasia involved many acini in some lobules. Here the spaces filled with desquamated epithelial cells, macrophages, giant cells, neutrophils and hyaline deposits with focal areas of frank oedema. Basophilic hyaline material also found. Mitotic figures common in the alveolar epithelium. Alveolar septa dilated by oedema and infiltrated by interstitial cells, neutrophils and eosinophils; few fine collagen strands sometimes noted. Interlobular septa contained gas, oedema fluid and occasional aggregates of plasma and lymphoid cells. Eosinophils sometimes numerous.</p>
Other Findings					Large mediastinal gas bullae. Mediastinal lymph nodes hyperplastic.

ANIMAL 31 AGE 8 SEX F BREED Blue/Grey					DATE OF EXAMINATION	August
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Small green-yellow mucous strands noted in the trachea.					Moderate interstitial emphysema (2+) recorded along with collapsed, reddish-brown lobules adjacent to these bullae.	
Most bronchi and bronchioles empty but a few contained a little free blood or a mixture of macrophages, neutrophils and eosinophils.					Mild pulmonary congestion and oedema confined to the ventro-caudal diaphragmatic lobes.	
Globule leucocytes numerous in the bronchial tree and many eosinophils found in and beneath the epithelium in the peribronchial connective tissue. Neutrophils common also and one focus of accumulation of these cells. Eosinophils and some plasma cells found about small blood vessels in the lamina propria.					Most lung lobules normal, histologically. A proportion (red-brown lobules) affected by focal oedema with fine hyaline membranes. Macrophages and desquamated epithelial cells were mixed with numerous neutrophils and giant cells in the lumen.	
Moderate neutrophil, eosinophil, plasma and lymphoid cell infiltration of the lamina propria of the bronchi.					Focal proliferation of alveolar epithelial cells in such lobules, particularly in alveoli at the edge of the lobule.	
Peribronchial cell infiltration was light.					Alveolar septa oedematous and fine collagen fibres could be distinguished. Many mononuclear cells, probably interstitial cells in the alveolar septa.	
In the apical lobes there tended to be more neutrophils in the bronchial and bronchiolar lumina.					Interlobular septa contained gas bullae, were oedematous and infiltrated by neutrophils, eosinophils and giant cells.	
A single adult <u>D. viviparus</u> was found in one section of bronchus.						

Other Findings Mild adult *Ostertagia burdens* were recorded. The mediastinal lymph nodes were enlarged.

ANIMAL 32 AGE A SEX F BREED Hereford					DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Small volume of white frothy fluid found in the trachea and bronchi. Most bronchi and bronchioles empty.					Apical, cardiac ventral diaphragmatic lobes fleshy, fawn coloured.	
A few contained neutrophils, macrophages and condensed hyaline deposits.					Other lobules pale pink, overinflated. Moderate interstitial emphysema (2+).	
Globule leucocytes numerous in the epithelium of trachea and bronchi. Neutrophils were common focally.					Desquamated mononuclear cells and giant cells filled many alveolar spaces. Condensed hyaline material also in the space or within phagocytes.	
Moderate lymphoid infiltration of the lamina propria with numerous neutrophils and a few eosinophils in the trachea and larger bronchi. Oedema of the lamina propria observed in some bronchi. Plasma and lymphoid cell infiltration of the peribronchial and peribronchiolar connective tissue was noticeable; in some acini there was extension of this infiltration into adjacent alveolar septa.					Neutrophils predominated in some alveoli. In a minority of acini, incorporation of intra-alveolar exudates into the alveolar septum and hyaline deposits. sometimes included. Widespread cuboidal epithelial cell hyperplasia; mitotic figures common intra-epithelially and in free cells.	
					Cuboidal layer covered organising intra-alveolar exudates also.	
					Alveolar septa dilated by oedema in some foci with increased collagen in others. Interstitial cells, neutrophils and eosinophils frequent; plasma cells and lymphocytes not common except near peribronchial and vascular connective tissue.	
					Interlobular septa dilated by gas.	
					Many lymphoid and plasma cells found in lymphatics. Giant cells frequent within and without lymphatics. Lymphoid and plasma cell infiltration of perivascular connective tissue.	

Other Findings Moderate burden of Ostertagia worms in the abomasum. Many petechial haemorrhages on the epicardium. Mediastinal lymph nodes hyperplastic.

					DATE OF	
ANIMAL	33	AGE	7	SEX	F	BREED
						Angus
					EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
Small volume white froth in the lobar bronchi.					The apical, cardiac and ventral diaphragmatic lobes were firm, rubbery and fawn-brown coloured.	
The weight of the lungs was 6800gm.					Marked subpleural emphysema and moderate interstitial emphysema (2+).	
A little oedema fluid containing macrophages and neutrophils found in many bronchi and bronchioles.					Mild oedema (1+) was found in the diaphragmatic lobes.	
Globule leucocytes frequent in the bronchial epithelium. Plasma cells, lymphocytes and neutrophils found in moderate numbers in the lamina propria and peribronchial connective tissue or occasionally in an intra-epithelial position.					Most lobules affected by alveolar epithelial hyperplasia and alveoli filled by hyaline deposits, desquamated cells, macrophages and a few neutrophils.	
					Pulmonary oedema and hyaline membranes frequent. Alveolar septa dilated by oedema and infiltrated by neutrophils.	
					Increased numbers of interstitial cells found. Light fibrosis seen focally.	
					Interlobular septa dilated by oedema fluid and contained gas bullae.	
					Plasma cells, lymphocytes, a small number of eosinophils and giant cells also apparent.	

Other Findings Traumatic reticulitis, peritonitis and adhesions.

					DATE OF	
ANIMAL	34	AGE	5	SEX	F	BREED
					EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	

A moderate volume of whitish froth found in the trachea and bronchi.
Most bronchi and bronchioles empty but a few contained some oedema fluid and macrophages. Globule leucocytes frequently found in the bronchial epithelium. A light plasma cell and lymphocyte infiltration of the lamina propria and peribronchial connective tissue.

Apical, cardiac and ventral diaphragmatic lobes fawn-brown, rubbery.
Severe interstitial emphysema (3+) and overinflation of dorsal apical and cardiac lobes.
Diffuse severe alveolar epithelial hyperplasia in most lobules in all lobes.
Alveoli filled by oedema fluid, condensed hyaline deposits, giant cells, foamy macrophages and very large numbers of desquamated epithelial cells. Alveolar walls lined by rows of cuboidal epithelial cells, some of which contained P.A.S. material in the cytoplasm.
Alveolar septa dilated by oedema and there were increased numbers of interstitial cells, neutrophils and a few eosinophils.
Slight increase in collagen in some septa but no increase in reticulin.
Interlobular septa contained gas, oedema and an infiltrate of giant cells, plasma cells, lymphocytes and macrophages.

Other Findings A large number of adult Fasciola hepatica were discovered in the liver. The mediastinal lymph nodes were enlarged and oedematous with frequent focal haemorrhages and gas bullae.

					DATE OF	
ANIMAL	35	AGE	5	SEX	F	BREED
						Hereford
					EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	

There was marked cyanosis.

Thin mucous strands noted in the trachea.

The right lung weighed 4700gm

" left " " 3500gm

8200gm

This cow was severely dyspnoeic and slaughtered on humane grounds. Some small bronchioles contained a little hyaline material or macrophages.

Globule leucocytes commonly found in the bronchial epithelium.

Light plasma cell, lymphocyte and neutrophil infiltration of the bronchial lamina propria and peribronchial connective tissue.

The lungs were very heavy, rubbery and coloured fawn-brown.

Almost all the lung was involved with the exception of the tips of the diaphragmatic lobes.

Moderate interstitial emphysema (2+) was noted. Pleural oedema confined to the posterior diaphragmatic lobes.

This animal was found to have the most extreme degree of alveolar epithelial hyperplasia encountered.

Almost the entire lung was affected and many alveoli and terminal bronchioles filled by sloughed cells.

Hyaline material commonly found in condensed bodies. Giant cells and a few neutrophils seen in the lumen.

Alveolar septa dilated by oedema and increased collagen focally.

Interstitial cells and neutrophils apparent in most places.

Interlobular septa dilated by oedema or gas bullae.

Eosinophils found in small numbers in alveolar septa and interlobular septa.

Other Findings Many petechiae were noted on the epicardium. The mediastinal lymph nodes were enlarged. Light Ostertagia and Fasciola adult burdens were found.

ANIMAL 36 AGE A SEX F BREED Shorthorn					DATE OF EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	
<p>No significant findings.</p> <p>Most bronchi and bronchioles empty, several obliterative lesions noted in mid-diaphragmatic lobes. Pus found in one focus of bronchitis. Many globule leucocytes in the epithelium and a few neutrophils, lymphocytes and plasma cells. Heavy plasma cell and lymphocyte infiltration of the lamina propria and peribronchial and peribronchiolar connective tissue; frequent aggregates of cells.</p>					<p>Moderate interstitial emphysema in the diaphragmatic lobes (2+) with frequent small bullae 4-5cm. in diameter.</p> <p>Fibrous tags on caudal edge of diaphragmatic lobes. Occasional fawn, firm lobules in all lobes.</p> <p>Most lobules overinflated but essentially normal: hypercellularity of the alveolar epithelium noticed. In some lobules alveolar epithelial hyperplasia over $\frac{1}{3}$-$\frac{1}{2}$ the acini and in these areas condensed hyaline material + giant cells in the lumen along with very many mononuclear cells, apparently from alveolar epithelium and neutrophils occasionally seen. Alveolar septa contained a few eosinophils and neutrophils and fine connective tissue strands of collagen and elastin, slightly in excess of normal.</p> <p>Interlobular septa were disrupted by gas bullae and many giant cells, neutrophils and some plasma and lymphoid cells found in the lymphatics.</p> <p>Many giant cells noted in the perivascular connective tissue of some pulmonary veins.</p>	

Other Findings A small number of adult Fasciola hepatica in the liver.
A small burden of Ostertagia worms in the abomasum.

						DATE OF			
ANIMAL	37	AGE	A	SEX	F	BREED	Blue/Grey	EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES							LUNGS		
No significant findings on gross examination.							Severe interstitial emphysema (3+), over-inflation of lung lobules in apical lobes. No pulmonary oedema.		
Most bronchi and bronchioles empty, but a minority contained small numbers of macrophages and a few neutrophils.							Most lung lobules fawn-brown, spongy in texture. Some lobules collapsed near gas bullae.		
Globule leucocytes very common in the bronchial epithelium.							Many lobules normal, others overinflated and some affected epithelial hyperplasia.		
Other intraepithelial cells mainly lymphocytes or plasma cells with a few eosinophils and neutrophils. Slight lamina propria oedema in some sections.							Alveolar epithelial hyperplasia extended over a part of some lobules, which sometimes collapsed. No complete lining in most alveoli (2+). Most alveolar spaces empty, but some contained macrophages or condensed eosinophilic hyaline deposits.		
Plasma and lymphoid cell infiltration light. Neutrophils found in some sites.							Some acini of some lobules found to have increased connective tissue in the alveolar septa. Partial epithelial hyperplasia in such acini and some were collapsed. Organisation of intra-alveolar exudate was taking place also. Small amounts of eosinophilic oedema precipitate noted in such acini.		
Little peribronchial or peribronchiolar lymphoid infiltration but increased connective tissue in many parts.							Some almost normal acini found to have hypercellularity of cuboidal epithelial cells. Many alveolar septa normal. Others contained increased connective tissue without infiltration by plasma cells, lymphocytes or eosinophils.		
Bulging of bronchiolar walls was seen in a few sites where muscle was absent.							Interstitial emphysema with focal fibrosis. Giant cells and a few eosinophils found.		
							A few eosinophils in lumen, wall and perivascular connective tissue in small veins.		
Other Findings							Mediastinal lymph nodes were hyperplastic.		

						DATE OF	
ANIMAL	38	AGE	5	SEX	F	BREED	Hereford
						EXAMINATION	September
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
No significant findings on gross inspection.						Pleural oedema and many fibrous tags over the posterior diaphragmatic lobes.	
The right lung weighed 2330gm						Small focal haemorrhages and greyish-	
" left " " 1630gm						brown spots frequent in scattered	
						lobules in all lobes.	
						Almost all lung lobules examined	
Globule leucocytes very frequent in the bronchial epithelium.						appeared normal.	
Lymphoid and plasma cell infiltration of lamina propria and						A minority contained some acini lined	
peribronchial connective tissue						by hyperplastic alveolar epithelial	
was light.						cells.	
						There was slight increase in alveolar	
						septal connective tissue in such	
						areas and a few neutrophils and	
						eosinophils found in the alveolar	
						wall and lumen.	

					DATE OF	
ANIMAL	39	AGE	A	SEX	F	BREED
					EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	

A small volume of whitish froth was confined to the lobar bronchi. Most bronchi and bronchioles empty although some small bronchioles contained muco-pus. In areas of alveolar epithelial hyperplasia there was oedema fluid, macrophages and neutrophils in the lumen. Globule leucocytes and neutrophils were numerous in the epithelium. Plasma cell and lymphocyte infiltration of the lamina propria was light and a similar infiltrate was noted in the peribronchial connective tissue.

Moderate interstitial emphysema (2+) with large bullae in the left diaphragmatic lobe recorded. Some lobules in all lobes fawn and firm but most were pale pink. The fawn lobules were the result of alveolar epithelial hyperplasia. Cuboidal epithelial cells lined most acini in such lobules and lay free (sometimes in large numbers) in the lumen with alveolar macrophages and neutrophils. Giant cells and aggregates of condensed hyaline material common in these acini. Alveolar septa were oedematous and contained neutrophils and many interstitial cells. Some fine collagen strands apparent focally. In a minority of alveoli there was incorporation of intra-alveolar exudates into the alveolar wall. Some hyperplastic acini were collapsed and markedly infiltrated by neutrophils. Many lobules were overinflated or apparently normal. Interlobular septa were dilated by gas in places or contained many plasma cells and lymphocytes with lesser numbers of eosinophils and neutrophils.

Other Findings A small number of adult Fasciola hepatica were found in the liver. A moderate Ostertagia worm burden was recorded in the abomasum.

						DATE OF	
ANIMAL	40	AGE	A	SEX	F	BREED	Blue/Grey
						EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
<p>A small volume of white frothy fluid was found in the trachea and bronchi.</p> <p>Most bronchi and bronchioles were empty, others contained a little oedema fluid and macrophages. Globule leucocytes numerous in the bronchial tree and a few intra-epithelial eosinophils. Plasma cells and lymphocytes together with a few eosinophils formed a light cellular infiltrate in the lamina propria and peribronchial connective tissue.</p>						<p>Severe interstitial emphysema (3+) with overinflation of many lung lobules recorded.</p> <p>Many scattered lung lobules were deep red-purple in colour with focal haemorrhages in some. In these red lobules focal oedema with many macrophages and desquamated epithelial cells in the alveolar spaces. Giant cells and organising intra-alveolar exudates were seen focally. In parts of some lobules areas of alveolar epithelial hyperplasia involving groups of acini; here the alveolar septa were thickened by oedema fluid and a cellular infiltration of neutrophils and interstitial cells.</p> <p>Giant cells and macrophages with a few eosinophils were noted in interlobular septa: the septa were dilated by gas and some oedema. Several small aggregates of lymphocytes up to 1mm. in diameter were seen in the lungs adjacent to terminal bronchioles.</p>	

Other Findings Mediastinal lymph nodes were enlarged and contained many gas bullae and focal haemorrhages. Light Fasciola hepatica burden in the liver.

ANIMAL 41 AGE A SEX F BREED Hereford						DATE OF EXAMINATION	October
TRACHEA, BRONCHI & BRONCHIOLES						LUNGS	
No significant findings on gross examination.						Apical and dorsal cardiac lobes were overinflated: moderate interstitial	
Most bronchi and bronchioles empty: a few contained a small number of macrophages and eosinophils.						emphysema was confined to the diaphragmatic lobes (2+).	
Many globule leucocytes were noted in the epithelium of trachea and bronchi.						Many lung lobules were collapsed around gas bullae.	
						Few lung lesions microscopically apart from focal overinflated or collapse, acini were normal in most parts.	
There was a light plasma and lymphoid cell infiltration of the lamina propria.						Eosinophils infiltrated the alveolar interstitium in many sites and these cells frequently found in the interlobular septa.	
Aggregates were infrequent.						Two granulomatous lesions were found about fungal clubs of aspergillus.	
Eosinophils were present in moderate numbers, especially around the mucous glands.						Eosinophils were particularly numerous in the alveoli and interstitial tissues about these lesions.	
The peribronchial connective tissue was lightly infiltrated by plasma and lymphoid cells.						Eosinophils were found in the lumen, wall and perivascular connective tissue of some small blood vessels.	
Eosinophils were frequent in the lymphoid aggregates occasionally observed.							
There was dilatation of the walls of small bronchioles where the muscle layer was absent. Many bronchioles were almost occluded (by contraction of the muscle) in areas of alveolar collapse.							
<u>Other Findings</u>						Mediastinal lymph nodes were hyperplastic. Bile duct fibrous.	

					DATE OF	
ANIMAL	42	AGE	A	SEX	F	BREED
					EXAMINATION	November
TRACHEA, BRONCHI & BRONCHIOLES					LUNGS	

The trachea and bronchi contained a few small greyish mucous globules.

Many globule leucocytes were found in the bronchial tree.

Lymphocyte and plasma cell infiltration of the lamina propria was moderate. The muscle layer of some smaller bronchioles appeared to be hypertrophied.

Peribronchial lymphoid accumulation was light.

The lungs appeared to be normal on gross inspection.

Histologically there are a very few acini in which the alveolar epithelium is hyperplastic with short rows of 4-6 cells lining part of the wall.

The vast majority of acini are normal. Giant cells and neutrophils form aggregates in the interlobular septa in places.

There were 1mm. diameter aggregates of lymphocytes and plasma cells in the acini adjacent to terminal bronchioles in 2 lung sections.

ANIMAL 43	AGE A	SEX F	BREED Shorthorn	DATE OF EXAMINATION	November
TRACHEA, BRONCHI & BRONCHIOLES				LUNGS	

The trachea, bronchi and bronchioles were empty except for occasional grey mucous globules. Many globule leucocytes were observed in the bronchial epithelium and there were frequent intra-epithelial neutrophils and lymphocytes.

Plasma cell and lymphocyte infiltration of lamina propria light. Neutrophils regularly noted but few in number.

Peribronchial cell infiltration sparse except for bronchioles in greyish-white lobules (q.v.).

Almost all the lungs unremarkable in appearance and the lobules appeared normal histologically apart from frequent giant cells, macrophages and neutrophils in the interlobular septa. Overinflation of apical and cardiac lobes.

A few scattered greyish-white lobules were recorded in all lobes and in these there is focal alveolar septal fibrosis.

There is hyperplasia of the alveolar epithelium in some parts of these areas also. A mononuclear cell infiltration of the peribronchiolar connective tissue heavy in places.

Other Findings Liver - some bile duct fibrosis.

APPENDIX 2

POSTMORTEM LESIONS IN CASES OF
DIFFUSE FIBROSING ALVEOLITIS

						Date of	
Animal	A	Age	Adult	Sex	F	Breed	Friesian Examination 8.11.72
Trachea, Bronchi and Bronchioles						Alveoli and Alveolar Septa	
Excess mucus was found in the trachea and bronchi, this was usually grey-green, but was often yellow in the segmental bronchi. Mucous plugs infiltrated by macrophages and neutrophils were seen in some bronchioles. Bronchiolitis obliterans was noted in several sections.						Lungs were very pale, overinflated, firm to cut and weighed 7400gm. Very fibrosed, yellowish lobules noted in the dorsal cardiac lobes; lobules of the right apical and ventral cardiac lobes were heavy, greyish-brown and oedematous. There was diffuse, mild pulmonary oedema. There were lesions in all lobes, but not all lobules were affected; many were normal.	
The bronchial epithelium was infiltrated by many neutrophils and eosinophils; globule leucocytes were frequent.						Affected acini were mainly empty; others contained oedema fluid, macrophages and a few neutrophils.	
There was a heavy plasma cell and lymphocyte infiltration of the lamina propria; neutrophils and eosinophils were common.						There was alveolar epithelial hyperplasia and focal columnar ciliated and mucous cell metaplasia.	
There was heavy plasma cell and lymphocyte infiltration of the peribronchial and bronchiolar connective tissue; many aggregates of cells were formed.						Alveolar septa were thickened, fibrosed and infiltrated by eosinophils, many plasma and lymphoid cells, often forming aggregates. Interlobular septa contained many eosinophils and in places were fibrosed.	

Other Findings Monolobular fibrosis in most liver lobes and severe scarring of the ventral lobe; the bile ducts were fibrosed and calcified. The pulmonary artery was dilated, though there was not obvious right ventricular hypertrophy. Multiple erosions and ulcers were found on the abomasal folds. A small number of haemosiderin bearing macrophages were found in the bronchial nodes.

Animal	B	Age	10y	Sex	F	Breed	Friesian	Date of Examination	9.11.71.
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Trachea, Bronchi and Bronchioles	Alveoli and Alveolar Septa
<p>Excess green-grey mucus found in the bronchi; yellow mucous plugs seen in smaller bronchi in some lobes.</p> <p>Most bronchi and bronchioles empty; mucus or pus found in a few.</p> <p>Organising intra-bronchiolar exudates common in some sections, where acini were overinflated.</p> <p>Globule leucocytes frequent in the bronchial epithelium; many neutrophils found there also.</p> <p>Heavy infiltration of plasma and lymphoid cells in the lamina propria and a moderate infiltrate of neutrophils. Eosinophils sparse.</p> <p>Some mucous glands dilated.</p> <p>Heavy plasma cell and lymphocyte infiltration of the peribronchial connective tissue, which was fibrosed.</p> <p>Proliferation of terminal bronchiolar epithelium to form papillary projections into the alveolar ducts and alveoli.</p>	<p>Lungs very pale pink, overinflated, very firm and heavy. Lobules in dorsal cardiac and diaphragmatic lobes yellowish and very fibrosed.</p> <p>Moderate pulmonary oedema.</p> <p>Most alveoli empty; but large mononuclear cells, neutrophils and giant cells in others. Many acini were overinflated.</p> <p>Many alveoli lined by cuboidal epithelial cells. Groups of acini lined by tall columnar ciliated and mucous cells; alveoli filled with mucus. Organising intra-alveolar exudates sometimes seen.</p> <p>Widespread, severe fibrosis of the alveolar septa, with usually only a few plasma cells or lymphocytes; in places the infiltration was heavy.</p> <p>Interlobular septa were fibrosed; mast cells were abundant here and in alveolar septa.</p> <p>There was intimal fibrosis in many blood vessels.</p>

Other Lesions This animal had developed cor pulmonale and was in congestive cardiac failure. The liver was affected by severe chronic venous congestion. There was bilateral renal amyloidosis and interstitial nephritis with fibrosis. Extensive fibrosis in the right hind quarter of the mammary gland was also recorded.

Animal	C	Age	Aged	Sex	F	Breed	Fr x	Ayr	Date of Autopsy
									1.3.72.

Lesions in Trachea, Bronchi & Bronchioles. Lesions in Alveoli, Alveolar Ducts

Many greenish-yellow mucous plugs found in trachea and lobar bronchi. Mucous plugs, infiltrated by neutrophils, macrophages and a small number of eosinophils found in the bronchi.	lung weight was 8100gm.
Frequent bronchiolitis obliterans. Globule leucocytes very frequently found in the epithelium; many intra-epithelial neutrophils.	Many lung lobules pale, overinflated and contained small grey spots. Some lobules greyish-red, slightly collapsed; on section clear fluid ran freely from the surface; these lobules mainly in anterior lobes.
Bronchitis and bronchiolitis; infiltration of lamina propria by neutrophils, plasma and lymphoid cells and a small number of eosinophils.	Some alveoli normal; others overinflated; others filled by precipitated oedema protein. Large mononuclear cells, eosinophils, neutrophils with some plasma cells and small lymphocytes found in lumen. Foci of alveolar epithelial metaplasia with alveoli filled with mucus.
Marked folding and papillary projection of the epithelium and lamina propria.	Alveolar epithelium was normal; hyperplastic; replaced by tall columnar ciliated cells; replaced by tall columnar ciliated and mucous cells.
Heavy infiltration of plasma and lymphoid cells in the peribronchial and bronchiolar connective tissue, peribronchial fibrosis and mucous gland hyperplasia.	Alveolar septa thickened by heavy infiltration of plasma and lymphoid cells; severe focal fibrosis. Interlobular septa often normal; but occasionally contained large aggregates of plasma and lymphoid cells.

Other Findings Cor pulmonale.

There was fibrosis of the bile ducts in the ventral lobe of the liver. Renal amyloidosis was also noted.

Animal D Age 8y Sex F Breed Galloway Date of Autopsy 28.1.72.

Trachea Bronchi and Bronchioles	Alveoli and Alveolar Ducts
<p>Many thick mucous plugs, often yellowish in colour, in trachea and lobar bronchi.</p> <p>Mucous plugs, infiltrated by neutrophils; pus; large obliterative lesions found in the lumen of bronchioles.</p> <p>Globule leucocytes frequent in the bronchial epithelium. Occasional neutrophils and lymphocytes noted intra-epithelially.</p> <p>Many plasma cells, lymphocytes and neutrophils in the lamina propria and this was thrown into deep folds.</p> <p>Peribronchial fibrosis and infiltration by lymphocytes and plasma cells.</p>	<p>Weight of the lungs was 7300gm.</p> <p>Lungs were very pale pink; many lobules were overinflated and contained many grey spots. Lobules in the dorsal apical and cardiac lobes very firm and yellow in colour.</p> <p>Occasional lobules depressed, greyish-red and oedematous.</p> <p>Some alveoli empty; others filled by cedema fluid, resolving hyaline deposits, many neutrophils and macrophages. In some acini there was marked large mononuclear cell accumulation.</p> <p>Alveolar epithelium was normal or hyperplastic; occasional foci of columnar ciliated cells.</p> <p>Many alveolar septa thickened by a massive infiltration of plasma and lymphoid cells; others distorted and thickened by fibrosis.</p>

Other Findings There was bile duct fibrosis and calcification; a few adult Fasciola hepatica were found.

Animal	E	Age	6y	Sex	F	Breed	Ayrshire	Date of Autopsy	5.9.71
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Trachea, Bronchi and Bronchioles

Small volume of white froth at the nares, in the trachea and bronchi. Small yellow mucous plugs frequent in bronchioles. Focal intra-bronchial and pulmonary haemorrhages. Mucous plugs and frank blood in the lumen of some bronchioles. Many globule leucocytes found in the bronchial epithelium, which was hyperplastic. Focal 'squamous metaplasia'. Plasma and lymphoid cell accumulation and constant infiltration of neutrophils and some eosinophils in the lamina propria. Peribronchial fibrosis and infiltration and aggregation of plasma and lymphoid cells, in moderate degree.

Acini and Interstitium

Lungs extremely heavy, weight 12kg. The lungs very firm, fleshy; on section contained little air or fluid. Lungs light brown in colour; bronchioles very prominent and greenish-grey. Severe (3+) interstitial emphysema and overinflation of apical lobes. Only a very few apparently normal lobules on gross inspection. Alveoli empty; filled by hyaline deposits, macrophages and neutrophils; oedema fluid; or a massive accumulation of large mononuclear cells. Widespread alveolar epithelial hyperplasia; double or triple layers of cells and many mitotic figures. Massive, diffuse alveolar septal fibrosis and a lesser degree of plasma, lymphoid and mast cell accumulation; eosinophils common. Interlobular septal fibrosis and lymphoid aggregate formation.

Other Lesions Mediastinal lymph nodes enlarged, oedematous and contained focal haemorrhages and gas bullae. Localised pleurisy of the left apical lobe.

						Date of
Animal	F	Age	7y	Sex	F	Breed
HxP	Examination	June 1, 1972				
Trachea, Bronchi and Bronchioles						Alveoli and Alveolar Septa
Small volume of white foam and a few mucous strands were found in the trachea and bronchi.						The lungs weighed 11,200gm. Most of lungs fawn-brown in colour, slightly oedematous and firm to cut. Some lobules contained small grey spots;
Mucus was found in many bronchi histologically. Organising intra-bronchial exudates were common.						dorsal diaphragmatic and cardiac lobes were yellowish and heavily fibrosed.
A very large number of globule leucocytes was noted in the epithelium.						Some normal acini but majority filled by many large mononuclear cells, giant cells or organising intra-alveolar exudates. Basophilic hyaline deposits frequent.
Lymphocytes were found in lesser numbers.						Widespread alveolar epithelial hyperplasia, 2-3 cells thick in places.
Many plasma cells and lymphocytes, with a moderate number of eosinophils were present in the lamina propria.						Columnar, ciliated and mucous secreting cells lined many alveoli.
There was heavy plasma cell and lymphocyte accumulation in the peribronchial connective tissue.						Dense infiltration of alveolar septa by plasma cells and lymphocytes with a few eosinophils and neutrophils; extensive mild septal fibrosis and oedema.
						Interlobular septa fibrosed and infiltrated by plasma and lymphoid cells.
						Intimal fibrosis in many pulmonary arterioles.

Other Findings

							Date of
Animal	G	Age	Aged	Sex	F	Breed	Highland Autopsy 13.3.72
Trachea, Bronchi and Bronchioles							Alveoli and Alveolar Septa
Many tenacious grey-green mucous plugs were found in the trachea and bronchi.							Lungs very pale pink, overinflated with fibrosis in many parts. Lungs weighed 4650gm.; heavy for such a small cow.
Mucous plugs were very frequent in histological sections. Organising intra-bronchial exudates were occasionally seen.							Many lobules in all lobes contained small grey spots.
Globule leucocytes were numerous. Intra-epithelial neutrophils were uncommon.							Many alveoli empty; some contained large mononuclear cells and a little oedema fluid; others contained mucus.
There was a constant infiltration of plasma cells and lymphocytes into the lamina propria and this was heavy in places.							Frequent alveolar epithelial hyperplasia or focal, columnar ciliated and mucous secreting cells.
The plasma cell and lymphocyte accumulations in the peribronchial connective tissue were focally very heavy and arranged in large aggregates.							Alveolar septal fibrosis present in most lobules, but often did not involve the whole lobule. Plasma cells and lymphocytes sometimes found in large numbers in the septa.
							Fibrosis of interlobular septa.
							Intimal fibrosis found in some pulmonary arterioles.

Other Lesions Cor pulmonale; pulmonary arterial dilatation, dilatation and thickening of the right ventricle.
Liver cirrhotic.

						Date of	
Animal	H	Age	Sex	F	Breed	Shorthorn	Autopsy 28.1.72
Trachea, Bronchi and Bronchioles						Alveoli and Alveolar Ducts	
Abundant clear mucus in the trachea and bronchi and plugs of mucous found in many bronchioles.						Lungs weighed 7kgm.	
Frequent obliterative lesions in the bronchioles.						Many lobules in all lobes of the lungs grey-red in colour and oedematous. Other lobules pale pink, very firm to cut; on section the bronchioles were greenish-grey in colour.	
Many globule leucocytes found in the epithelium which was hyperplastic and had, focally, undergone 'squamous' metaplasia'.						Focal oedema and hyaline deposits in some alveoli. Others were filled by exceedingly large numbers of large mononuclear cells. Frequent alveolar epithelial hyperplasia.	
Infiltration of lamina propria by lymphocytes and plasma cells; many neutrophils below and between epithelial cells.						Very severe, widespread fibrosis of alveolar septa and a constant, moderate, infiltration of lymphoid and plasma cells.	
Plasma and lymphoid cell infiltration of the peribronchial connective tissue, which was thickened by fibrosis.						Interlobular septa fibrosed with aggregates of lymphocytes and plasma cells.	

Fibrosis and thickening of bile ducts, severe fibrosis of ventral lobe, widespread monolobular fibrosis, results of Fasciola hepatica infestation. Proliferative glomerulonephritis with glomerulosclerosis, mesangial thickening and increased numbers of mesangial cells.

Date of									
Animal	J	Age	3y	Sex	F	Breed	Gall	x Sh	Autopsy 6.7.72
Trachea, Bronchi and Bronchioles					Alveoli and Alveolar Septa				
<p>Large volume greyish-green mucus in trachea and bronchi; frequent green strands of mucus in small bronchi. Wedge shaped area of collapse associated with bronchial blockage by mucus in right diaphragmatic lobe. Mucus or pus in the lumen in some sections, but most bronchi and bronchioles empty.</p> <p>Globule leucocytes neutrophils, eosinophils frequent in the epithelium, although few neutrophils free in the lumen.</p> <p>Heavy plasma cell and lymphocyte infiltration of the lamina propria; neutrophils and eosinophils common. Mucous glands hyperplastic.</p> <p>Plasma cell and lymphocyte infiltration about the bronchi and some bronchioles and peribronchial fibrosis.</p>					<p>Lungs very pale, firm and heavy; weight 7kgm.</p> <p>Apical lobes overinflated; many lobules in other lobes pale pink with depressed grey foci. Fibrosis not as extensive as most severe cases.</p> <p>Most alveoli empty, many over-inflated. Macrophages, neutrophils and eosinophils found in others. Widespread alveolar epithelial hyperplasia; focal ciliated or mucous cell metaplasia.</p> <p>Diffuse, moderate, alveolar septal fibrosis and small infiltrate of plasma and lymphoid cells and eosinophils. Focally, cell influx heavy and aggregates found, especially near periphery of lobule.</p> <p>Alveolar duct smooth muscle thickened.</p> <p>Fibrosis of interlobular septa and accumulations of eosinophils.</p> <p>A granuloma with large giant cells found in perivascular connective tissue of the pulmonary artery in one section.</p>				

Other Findings The pulmonary trunk was dilated, although there was no obvious increase in ventricular muscle mass.

Animal	K	Age	6y	Sex	F	Breed	Friesian	Date of Examination	March
Trachea, Bronchi and Bronchioles								Acini	
<p>Excess, thick mucopurulent exudate found in trachea and bronchi; plugs of mucus noted in smaller bronchi. Pus discovered in smaller bronchi of apical lobes.</p> <p>Abundant mucus could be seen in many histological sections and was frequently infiltrated by macrophages, polymorphs and some giant cells.</p> <p>Organising intra-bronchial exudates were common and the same process could be observed in some alveoli and alveolar ducts. Globule leucocytes were frequent in the bronchial epithelium and there was a heavy plasma and lymphoid cell infiltration of the lamina propria and peribronchial connective tissue. Eosinophils were found in moderate numbers.</p>								<p>Lungs very pale, heavy and much firmer than normal to cut. Obvious diffuse increase in fibrous tissue; parts of diaphragmatic lobes had undergone cystic change.</p> <p>Anthracosis noted in many areas. Many small bullae of air in interstitium of diaphragmatic lobes. Large mononuclear cells filled alveolar spaces. Alveolar epithelial hyperplasia common; also ciliated or mucous secreting cells in many alveoli; there was mucus in the lumen, even where no mucus secreting cells were in the epithelium.</p> <p>Oedema of alveoli and terminal bronchioles, smooth muscle hypertrophy in alveolar ducts and foci of bronchopneumonia.</p> <p>Extensive fibrosis of alveolar septa, many dense accumulations of plasma and lymphoid cells. Haemosiderin and carbon bearing macrophages in the septa. Fibrosis marked in areas of cystic change where lung architecture destroyed.</p>	

Other Lesions Fibrosis and thickening of bile ducts in the liver; attributed to Fasciola hepatica infestation.

APPENDIX 3POSTMORTEM LESIONS IN ANIMALS IN THEIR FIRST GRAZING SEASON

ANIMAL	4	AGE	10M	SEX	M	BREED	IBER x	DATE EXAMINED	OCT. '70
History	<p>This calf was one of a group of 20 which had been at pasture in a large field, grazed by bulling heifers and calves the autumn before. These 20 calves were dosed with 'Thibenzole' in late July but remained on the same field. This one was noticed to be ill and was treated for 'pneumonia' with antibiotics and corticosteroids about a week after being brought indoors into an open court.</p> <p>The farmer claimed that he had vaccinated all the calves with 'Dictol'.</p>								
Post-mortem findings	<p>At autopsy, 150 adult worms were recovered from the bronchial tree. There were a large number of consolidated areas in each lung and alveolar epithelial hyperplasia affected portions of the diaphragmatic lobes.</p> <p>Adult worms were frequently found in histological sections and there was extensive, marked bronchitis, bronchiolitis and bronchiolitis obliterans. Neutrophil, eosinophil and macrophage exudate was noted in many acini and pulmonary oedema and hyaline membranes were found focally. Globule leucocytes were not found.</p>								

ANIMAL	21	AGE	9M	SEX	M	BREED	FR x	DATE EXAMINED	NOV. 70.
History	<p>This was one of a group of 20 similar calves grazing on the same field all summer; all had been vaccinated, since parasitic bronchitis had been a problem in the past.</p> <p>The calves were all taken inside on 2.11.70 into an open court and on 3.11.70 this calf developed acute respiratory distress. It was the only animal affected, although many others were coughing.</p> <p>This calf was dyspnoeic, coughing, tachypnoeic and pyrexia. It died on 6.11.70 despite repeated therapy with 'Nemicide'* and dexamethasone.</p>								
Post-mortem findings	<p>No adult lungworms were found in the trachea and Baermann examination was negative.</p> <p>Mucus plugs and some free blood were found in the congested bronchi. All the lungs were affected by alveolar epithelial hyperplasia with the exception of the overdistended dorsal apical lobes; the lungs were rubbery and firm but dark red with congestion rather than fawn. Moderate oedema and interstitial emphysema were present.</p> <p>Pulmonary oedema and hyaline membranes and short rows of hyperplastic alveolar epithelial cells were present in all sections. There was bronchitis and bronchiolitis and very occasionally bronchiolitis obliterans. Globule leucocytes were infrequent.</p> <p>Homogenous, eosinophilic bodies, possibly fragments of parasites were found in one section of bronchus.</p>								

*Nemicide - levamisole hydrochloride (I.C.I.)

ANIMAL	22	AGE	9M	SEX	F	BREED	SH x	DATE EXAMINED	SEPT. 69.
History	<p>This calf was one of a group of 35 similar calves which grazed permanent calf paddocks during the summer. There was sporadic coughing in all the calves, which were unvaccinated, during the autumn, but none were treated for husk. Three days after movement into an open court this one became dyspnoeic and was submitted to us. Other animals recovered after treatment with antibiotics, corticosteroids and 'Franocide'*. </p>								
Post-mortem findings	<p>No lungworms were found in the trachea and bronchi and Baermann examination was negative. The apical and cardiac lobes were fawn in colour and rubbery in consistency.</p> <p>The remaining lung was overinflated and there was mild interstitial emphysema(1+). Groups of lobules 2x2cm in size at the posterior edge of each diaphragmatic lobe were consolidated. Bronchitis, bronchiolitis and bronchiolitis obliterans, associated with overinflated acini, were frequently found. There was bronchiolar epithelial hyperplasia and squamous metaplasia. Adult lungworms were found in sections of small bronchi and there were aggregates of lymphocytes about fragments of parasites in the bronchioles. Globule leucocytes were infrequent.</p>								

* Franocide - diethylcarbamazine citrate (B.W. & Co.).

APPENDIX 4ANIMALS IN THEIR SECOND GRAZING SEASON:HISTORY AND POSTMORTEM FINDINGS

Animal	A	Age	15M	Sex	F	Breed	Her x	Date Examined	October
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On this farm, there was a respiratory disease in the autumn involving two groups of unvaccinated, Hereford cross calves, (68 heifers and 56 steers), which were run separately.

In early September, the heifers were placed on a permanent grass field and coughing was noticed in many animals 2-3 weeks later. These cattle were treated with 'Nemicide' on 29th September and were moved to a fresh, fertilised, aftermath paddock.

The steers were also moved to a fresh permanent pasture at the end of August and coughing began amongst them. They were all treated with 'Nemicide' in mid-September - i.e. about 14 days before the heifers.

Two steers died, one 10 days after the move to fresh pasture and the other 30 days after the move and 7 days after 'Nemicide' treatment; neither animal was postmortemed.

Two heifers were very dyspnoeic and pyrexia on 24.10.70. but responded to treatment with antibiotics and corticosteroids over the following 5 days. Two more heifers became dyspnoeic on 26.10.70 and one rapidly died, the other one was submitted to us for diagnosis on 28.10.70, about 55-60 days after the first move to fresh pasture.

Physical examination indicated that this heifer was grossly dyspnoeic, recumbent and near to death. There was marked cyanosis.

Examination of the rest of the herd revealed tachypnoea (respiratory rates 40-80 per minute) in the majority of animals and many were coughing.

Animal	A	Age	15M	Sex	F	Breed	Her x	Date Examined	Oct. 70
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A small volume of froth and some thick, greenish, mucous strands were found in the trachea and bronchi; no adult lungworms were discovered and Baermann examination was negative.

The lungs were fawn-brown in colour over almost their entire surface and the lobes were rubbery in texture, except the dorsal apical lobes which were largely normal. This extreme degree of alveolar epithelial hyperplasia was reflected in the histological appearance - almost all alveoli were lined by cuboidal epithelial cells (grade 3+) and there were many similar cells in the lumen. Hyaline membranes and mild, focal pulmonary oedema were frequently seen. Interstitial emphysema was mild.

The bronchial epithelium was hyperplastic and only a few globule leucocytes were present. Acinar overinflation was often associated with either bronchiolitis obliterans or blockage of bronchioles by plugs of neutrophils and basophilic hyaline deposits. Bronchiolitis and bronchitis were common.

Parasitic debris was found in a number of histological sections.

Animal	B	Age	18M	Sex	F	Breed	Her x	Date Examined	16.10.70
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This heifer was not vaccinated against husk and had been treated for this disease in the autumn of 1969, when it was first at grass.

Only the early calves on this farm were given 'Dictol'.

The farmer needed to treat some calves for husk each year, but had not thought any required dosing in 1970.

The cattle were grazing a 4 year old temporary ley, half of which was aftermath, and had been on the field 4-6 weeks, although they had access to one part for only the last 14 days. This heifer was seen to be 'puffing' on 13.10.70 and was worse on 14.10.70. The farmer thought it was a case of husk, although it was not coughing; when the veterinary surgeon arrived, he gave antibiotics, antihistaminics, corticosteroids and Franocide on 14.10.70, 15.10.70 and 16.10.70.

There was no improvement and the animal was submitted.

She was slightly better when examined here; tachypnoea, and expiratory grunt were noted, but there was no pyrexia or coughing.

This animal improved before slaughter on 19.10.70, although it was always tachypnoeic.

Animal	B	Age	18M.	Sex	F	Breed	Her x	Date Examined	19.10.70
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A small volume of white foam was found in the trachea and bronchi but no lungworms were found and none were recovered on Baermann examination.

Almost all the lung lobes were fawn-brown in colour and rubbery in texture -- the result of diffuse alveolar epithelial hyperplasia. There was marked interstitial emphysema (2+) in the dorsal diaphragmatic lobes and there was overinflation of the dorsal apical lobes. Pulmonary oedema was mild. The hyperplastic mediastinal lymph nodes contained gas bullae and focal haemorrhages.

Cuboidal epithelial cells lined most alveoli, and similar cells were found in the lumen, along with hyaline deposits, engorged macrophages and giant cells. There was marked bronchitis and bronchiolitis and bronchiolitis obliterans was noted in several sections. Globule leucocytes were very frequent in the bronchial tree, except where the epithelium was 'tattered'.

Animal	C	Age	18M	Sex	F	Breed	Her x	Date Examined	Oct. 70
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This heifer was one of a group of 8 bought in a market in March 1970 to fatten at grass; none of the 8 thrived on this farm. The farmer had only been in the farm since March 1970 and any parasitic problems of the farm were not known.

This group were grazing a 2nd year ley all summer and from late September moved around stubble fields eating dykeside grass and any uncut barley. Turnips were fed in the field for one week, then they were all moved indoors and put on self-feed silage, on 26.10.70.

None of the group were coughing in the summer and only this one was ever ill indoors.

At 7.30 a.m. on 27.10.70, the farmer looked at the cattle and they appeared normal. At 8.30 a.m. a farm worker heard this heifer grunting and the vet was called, since the heifer was mistaken for a newly bought in animal and the farmer thought it was a case of 'transit fever'.

At 11.50 a.m. the heifer was very dyspnoeic, grunting on expiration, frothing at the mouth, tachypnoeic and hyperpnoeic. The veterinary surgeon considered the case was hopeless; ten minutes later the heifer was dead.

Animal	C	Age	18M	Sex	F	Breed	Her.X	Date examined	28.10.70.
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Some thin, clear mucus was found in the trachea: a small volume of blood tinged froth was present in the lobar and segmental bronchi. The larynx, trachea and lobar bronchi were deeply congested and contained many petechial haemorrhages. Adult lungworms were not discovered, and none were recovered after Baermann examination.

Both lungs were reddish-fawn in colour and rubbery in consistency.

After cross section, all lobules were similar in appearance; the cut surface was smooth, fawn in colour and released small quantities of oedema fluid under light pressure. Bullae of gas were found in the interlobular septa, and there was moderate (2+) interstitial emphysema. Pulmonary oedema was obvious in the dorsal diaphragmatic lobes and thick, yellow gelatinous oedema fluid lay in many interlobular septa.

Diffuse, severe alveolar epithelial hyperplasia was confirmed on histological examination in most lobules; tissue from the dorsal diaphragmatic lobes was affected by pulmonary oedema with hyaline membranes. Large mononuclear cells accumulated in the alveolar spaces. Clumped hyaline deposits, macrophages, eosinophils, neutrophils and multinucleated giant cells were also found in the lumen. Alveolar capillaries were very congested and the alveolar septa were focally oedematous and an increased number of interstitial cells was apparent at such sites. Eosinophils were numerous in the alveolar spaces, septa and interlobular septa. Globule leucocytes were infrequent in the bronchial tree. Bronchiolitis and bronchitis were present, but bronchiolitis obliterans was not identified in 80 blocks of lung tissue.

APPENDIX 5POSTMORTEM LESIONS IN INDOOR CALVES

PULMONARY LESIONS IN INDOOR CALVESANIMAL 1Gross pathology

Small volume of white froth in trachea and bronchi. Single 2x3cm subepithelial haemorrhage in dorsal, posterior trachea. Segmental bronchi in ventral, apical and cardiac lobes contained a little pus. Moderately severe interstitial emphysema (2+) with pulmonary oedema (2+). Apical, cardiac and ventral diaphragmatic lobes firm, dark red-purple and of smooth, shiny cut section. Collapsed, consolidated lobules in bronchopneumonic areas. Lungs only submitted.

Histopathology

Marked pulmonary oedema, prominent hyaline membranes (2+). Congestion of alveolar capillaries and extensive alveolar epithelial hyperplasia (Grade 2+). Bronchioles filled with desquamated epithelial cells, macrophages and oedema fluid. Oedematous interlobular septa with gas bullae. Bronchiolitis in most lobules with simple bronchopneumonia in others.

ANIMAL 2Gross pathology

Small volume white froth in airways. Deep congestion with petechial haemorrhages in trachea and bronchi. Lung lobules in all lobes were dark red-purple in colour, and congested with a smooth, glistening cut surface. Focal haemorrhages were seen in some lobules. Moderate pulmonary oedema (2+) and severe interstitial emphysema (3+) with many bullae were present in all lobes. Haemorrhage and gas bullae in mediastinal lymph nodes.

Histopathology

Bronchitis and bronchiolitis with occasional bronchopneumonia. Congestion and intra-alveolar haemorrhage; thin hyaline membranes (1+), multinucleated giant cells, alveolar macrophages and oedema in alveoli. Alveolar epithelial hyperplasia (2+) especially in apical lobes. Oedema and gas bullae in interlobular septa.

ANIMAL 3Gross pathology

Deep congestion of trachea and bronchi with many petechial haemorrhages. Small volume of oedema fluid in bronchi. All lung lobules were deep red-purple in colour, and exuded copious oedema fluid on section. Cut surface was smooth and glistening. Oedema (2+) and severe interstitial emphysema (3+) were recorded. Enlarged, oedematous mediastinal lymph nodes, with gas bullae and focal haemorrhages. Lungs only submitted.

Histopathology

Moderate pulmonary oedema with hyaline membranes (1+) and early alveolar epithelial hyperplasia (1+) were found, along with a mild bronchopneumonia.

ANIMAL 4Gross pathology

Moderate volume of white foam with small yellow pus plugs in trachea and lobar bronchi. Bronchiectasis in right apical, cardiac and both dorsal diaphragmatic lobes. Severe purulent bronchopneumonia of right apical lobe. Many small abscesses in all lobes, especially right cardiac. Pleurisy on right side. Very severe interstitial emphysema in anterior half of lungs. Gas bullae in mediastinum and subcutaneously on back, brisket and thorax.

Histopathology

Severe purulent bronchopneumonia with lung abscesses.

ANIMAL 5Gross pathology

Abundant white froth in lobar bronchi. Small ulcer on epiglottis. Many lung lobules were fawn-brown in colour, rubbery and contained little air; the cut surface was smooth and homogenous. Reddish brown wedge of pulmonary collapse associated with thickened bronchioles plugged with greenish pus. Emphysema absent. Fibrous tags on visceral pleura of diaphragmatic lobes. Enlarged mediastinal lymph nodes.

Histopathology

Very extensive alveolar epithelial hyperplasia (3+) with septal thickening and filling of alveolar spaces by many large mononuclear cells, giant cells and hyaline membranes (2+). Oedema was mild (1+). Bronchitis and bronchiolitis with bronchiolitis obliterans in many sections.

ANIMAL 6Gross pathology

Abundant white frothy fluid in trachea and bronchi. All lungs deep red-purple in colour, rubbery and heavy. Cut surface smooth, glistening; oedema fluid was easily expressed. Interstitial emphysema (1+) in diaphragmatic and apical lobes. Very few spongy, pink lobules. Fibrous pleural tags over diaphragmatic lobes. Pulmonary oedema graded 2+. Lymph nodes enlarged and oedematous.

Histopathology

Severe pulmonary oedema, extensive hyaline membranes (2+), congestion and alveolar epithelial hyperplasia (3+) in all lobes. Many large mononuclear cells in the lumen. Bronchitis and bronchiolitis.

ANIMAL 6Gross pathology

Abundant white frothy fluid in trachea and bronchi. All lungs deep red-purple in colour, rubbery and heavy. Cut surface smooth, glistening; oedema fluid was easily expressed. Interstitial emphysema (1+) in diaphragmatic and apical lobes. Very few spongy, pink lobules. Fibrous pleural tags over diaphragmatic lobes. Pulmonary oedema graded 2+. Lymph nodes enlarged and oedematous.

Histopathology

Severe pulmonary oedema, extensive hyaline membranes (2+), congestion and alveolar epithelial hyperplasia (3+) in all lobes. Many large mononuclear cells in the lumen. Bronchitis and bronchiolitis.

ANIMAL 7Gross pathology

Thick, grey mucous plugs in right apical lobar bronchus. Large volume yellow catarrhal exudate in lobar and segmental bronchi of diaphragmatic lobes. Right apical lobe collapsed and consolidated - grey in colour. Scattered lobules of red-brown consolidation in diaphragmatic lobes. Overinflated segments in cardiac and diaphragmatic lobes. Twelve pulmonary lymphoid nodules, some with grey-green centres. Mild interstitial nephritis.

Histopathology

APICAL LOBE: bronchitis, bronchiolitis and bronchopneumonia with bronchiolitis obliterans. DIAPHRAGMATIC LOBE: bronchitis, bronchiolitis and bronchopneumonia with eosinophils frequently present in bronchiolar exudate and alveoli. Collapsed alveoli filled with macrophages, some oedema, fine hyaline membranes and focal hypercellularity of alveolar wall.

ANIMAL 8Gross pathology

A large volume of yellow catarrhal exudate in trachea, lobar and segmental bronchi. Small, yellow-green mucous plugs in bronchioles. Congestion and consolidation of right apical and cardiac lobes. Scattered lobules in diaphragmatic lobes were reddish brown in colour with fine petechial haemorrhages and peripheral overdistension. No pulmonary lymphoid nodules were found.

Histonathology

Severe purulent bronchopneumonia in apical and cardiac lobes. Lobules in diaphragmatic lobes contained macrophages, giant cells, hyaline membranes and neutrophils with alveolar epithelial hyperplasia (1+). Alveolar septa were oedematous and contained more obvious interstitial cells.

ANIMAL 9Gross pathology

Deep congestion of trachea and bronchi. Segmental bronchi contained thin yellow exudate. Right apical and both cardiac lobes were deep purple in colour, very heavy, with deep congestion and a smooth glistening surface. Pulmonary oedema (1+) and mild interstitial emphysema (2+) were present in apical and diaphragmatic lobes. Single small 1-2cm diameter abscesses in apical and cardiac lobes.

Histopathology

Severe acute bronchopneumonia of apical and cardiac lobes. Prominent hyaline membranes in alveoli and alveolar ducts with focal oedema and intra-alveolar haemorrhage. Early bronchopneumonia in diaphragmatic lobes.

ANIMAL 10Gross pathology

"The trachea, bronchi and larger bronchioles contained a blood stained frothy exudate". "Plum coloured consolidation over apical and cardiac lobes of lung and along antero-ventral portion of the diaphragmatic lobes indicating a proliferative pneumonia." Widespread emphysema involving the remaining portions of lung tissue, the mediastinum and the mediastinal lymph nodes.

Histopathology

Severe widespread alveolar oedema with prominent hyaline membranes. Some alveoli contained many large mononuclear cells and an occasional giant cell, while others were filled with neutrophils. Congestion, oedema and intra-alveolar haemorrhage were also seen. Short rows of hyperplastic alveolar epithelial cells (1+) and eosinophils in alveoli and bronchioles.

ANIMAL 11Gross pathology

Histopathology Bronchopneumonia in apical and diaphragmatic lobes. Fungal colonies, resembling Aspergillus in bronchial and bronchiolar lumen along with mucous plugs, neutrophils and eosinophils. Little alveolar reaction - focal alveolar septal congestion, alveolar oedema, intra-alveolar haemorrhage and overinflation of peripheral alveoli.

ANIMAL 12Gross pathology

Histopathology Marked alveolar septal congestion and intra-alveolar haemorrhage. Prominent hyaline membranes and pulmonary oedema in many alveoli, basophilic streaking of hyaline membranes in alveolar ducts and bronchioles along with giant cells and macrophages containing hyaline membrane material. Flattened ribbons of hyperplastic epithelial cells (1+) lined many alveoli or were raised above the alveolar surface and detached. Plasma cells, lymphocytes and eosinophils in lymphatics of interlobular septa.

ANIMAL 13

Large pulmonary abscess replacing right diaphragmatic lobe.

Multiple small abscesses in other lobes. Scattered pulmonary lymphoid nodules in left lung lobes.

FOG FEVER AND ACUTE RESPIRATORY
DISTRESS SYNDROMES OF CATTLE

A summary of a thesis submitted for the
degree of Ph. D. in the faculty of
Veterinary Medicine of the University
of Glasgow by Roger G. Breeze, 1973.

The primary purpose of this study was to identify the causes of acute respiratory distress in cattle and to define the pulmonary disease known as fog fever. A clinical and pathological field survey of acute respiratory distress syndromes in cattle was conducted during the years 1969-1972 and the main respiratory disorders of adult cattle were discovered. In addition, an ultrastructural and histochemical investigation was made to determine the structure of the normal bovine lung and of the alveolar wall in fog fever, since existing reports of the normal lung architecture in cattle were inadequate and there had been no electron microscopical study of fog fever. Finally, several experiments were conducted in order to investigate the aetiology of fog fever and the pathogenesis of the pulmonary lesions.

In the first part of the thesis, the results of the clinical and pathological field survey are presented and the main pulmonary diseases of cattle are described, largely in pathological terms. Several of these diseases had not been identified or fully defined before this investigation.

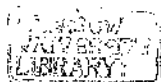
The ultrastructural and histochemical studies of the normal bovine lung are presented in the second part of the thesis. Although there have been previous reports of the electron microscopical appearance of the lungs of cattle, not all the cell types had been identified and the nomenclature was confused. In this section, there is also the first description of the fine structure of the alveolar wall in fog fever.

Several workers have suggested that fog fever is a hypersensitivity reaction to Dictyocaulus viviparus and in the third section, there is an experimental investigation of this hypothesis.

In this study, recovered cases of fog fever were challenged with infective third stage larvae of D. viviparus and with antigens derived from this parasite. It was concluded, from the results of these experiments, that there was no evidence to support the hypothesis.

Pulmonary lesions comparable to those of fog fever have been produced in cattle by the administration of DL - or L- tryptophan, 3 methyl-indole and indoleacetic acid. In the fourth section of the thesis, further experiments with these compounds are described and the relationship between fog fever and this experimental lung disease are examined.

Bordetella pertussis suspension has been used as an adjuvant in the production of reaginic antibodies. A preliminary investigation of the actions of this suspension in calves resulted in an acute respiratory distress syndrome which, in one instance, was accompanied by pulmonary lesions comparable to those of fog fever. The results and significance of this experiment are described in the final section.



library

FOG FEVER AND ACUTE RESPIRATORY

DISTRESS SYNDROMES OF CATTLE

BY

ROGER G. BREEZE, B.V.M.S., M.R.C.V.S.

Thesis submitted for the degree of Ph. D. in the
Faculty of Veterinary Medicine, the University
of Glasgow.

1973.

Thesis
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FIGURES FOR MACROSCOPIC AND HISTOPATHOLOGICAL LESIONS:

FIELD STUDY

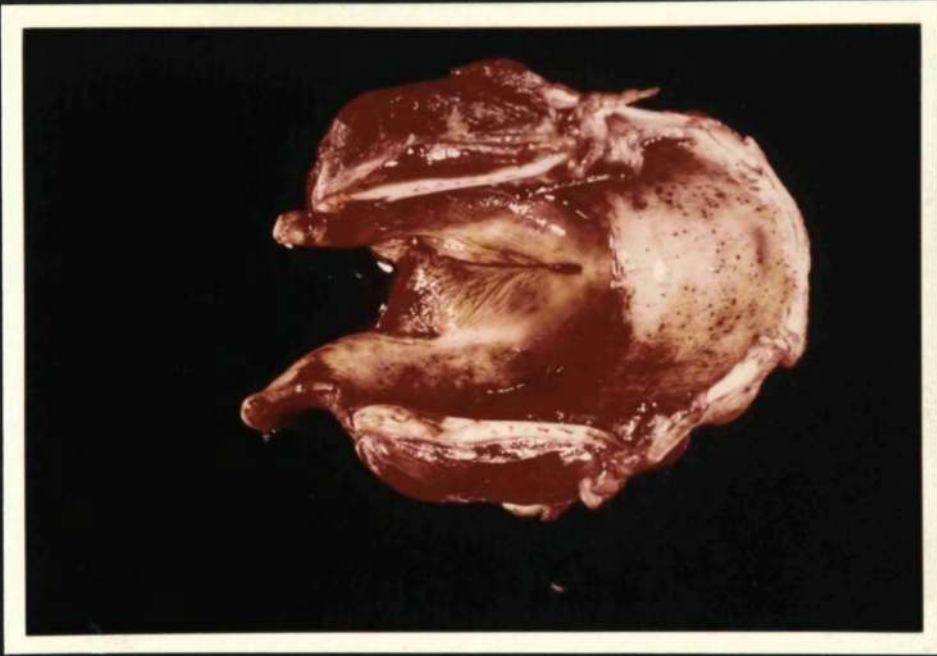
Fig. 8 Fog fever: congestion and very many petechial

haemorrhages, sometimes coalescent, in the larynx
of a fatal case.

Fig. 9 Fog fever: congestion and petechial haemorrhages in

trachea of fatal case. Focal haemorrhages between
cartilage rings (top right).

8



9



Fig. 10 Fog fever: lymphocytes in bronchial epithelium with oedema and lymphocyte and plasma cell infiltration of the lamina propria.

(H+E, x 500)

Fig. 11 Fog fever: oedema of the lamina propria of a bronchiole and peribronchiolar accumulation of lymphocytes and plasma cells. There is proliferation of alveolar epithelial cells (1+) with oedema and hyaline membrane material in the alveolar spaces.

(H+E, x 300)

10



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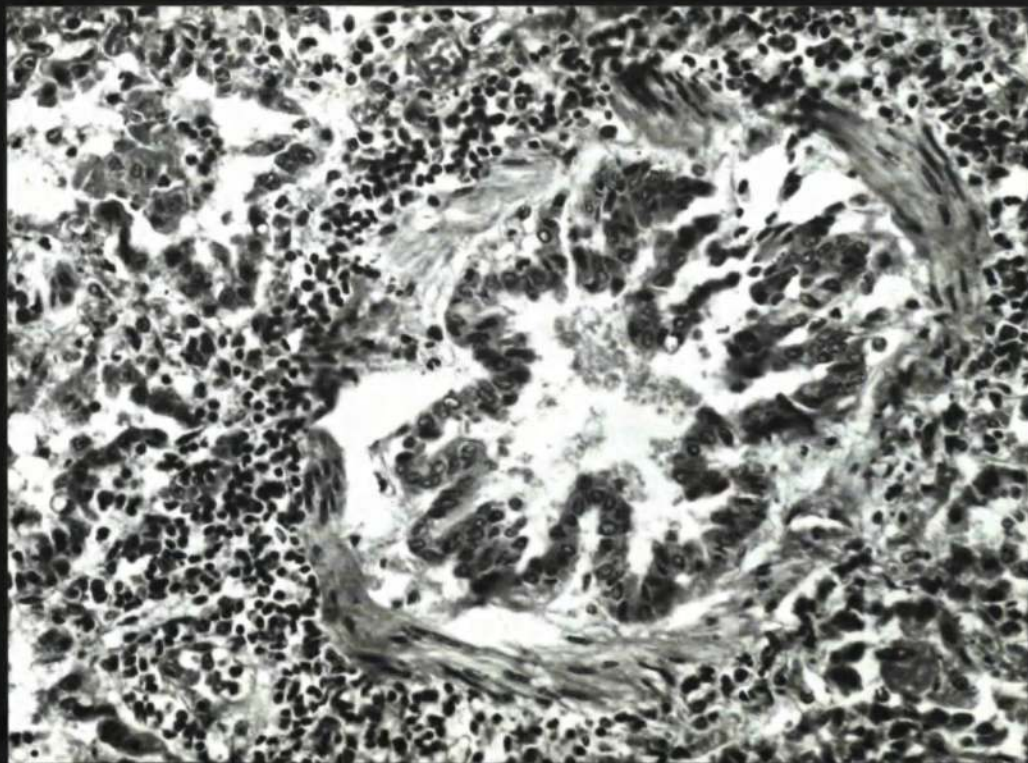


Fig. 12 Fog fever: loss of muscle coat over a segment of the wall of a bronchiole with attenuation of the epithelium and peribronchiolar aggregation and infiltration of plasma cells and lymphocytes. Macrophages and neutrophils are present in the bronchiolar lumen.

(H+E, x 110)

Fig. 13 Fog fever: overinflation of acini.

(H+E, x 110)

12



13

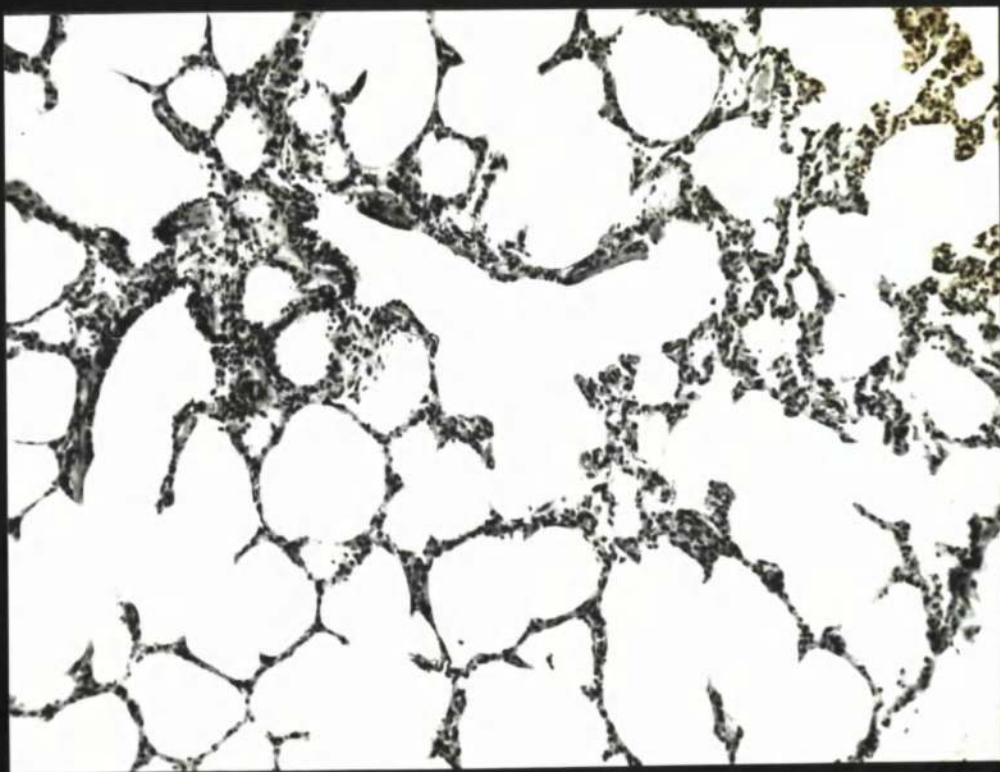


Fig. 14 Fog fever: dark red apical, cardiac and ventral

diaphragmatic lobes, the result of congestion, pulmonary oedema and hyaline membranes. Pleural oedema and severe interstitial emphysema in diaphragmatic lobes - note large gas bullae in mid-lobe.

(lungs of fatal case)

Fig. 15 Fog fever: cross section of diaphragmatic lobe of lungs

in Fig. 14 illustrating severe interstitial emphysema shiny, smooth, red lung lobules, the result of pulmonary oedema and hyaline membranes with congestion.

14



15



Fig. 16 Fog fever: effect of overinflation and severe interstitial emphysema on individual lung lobules.

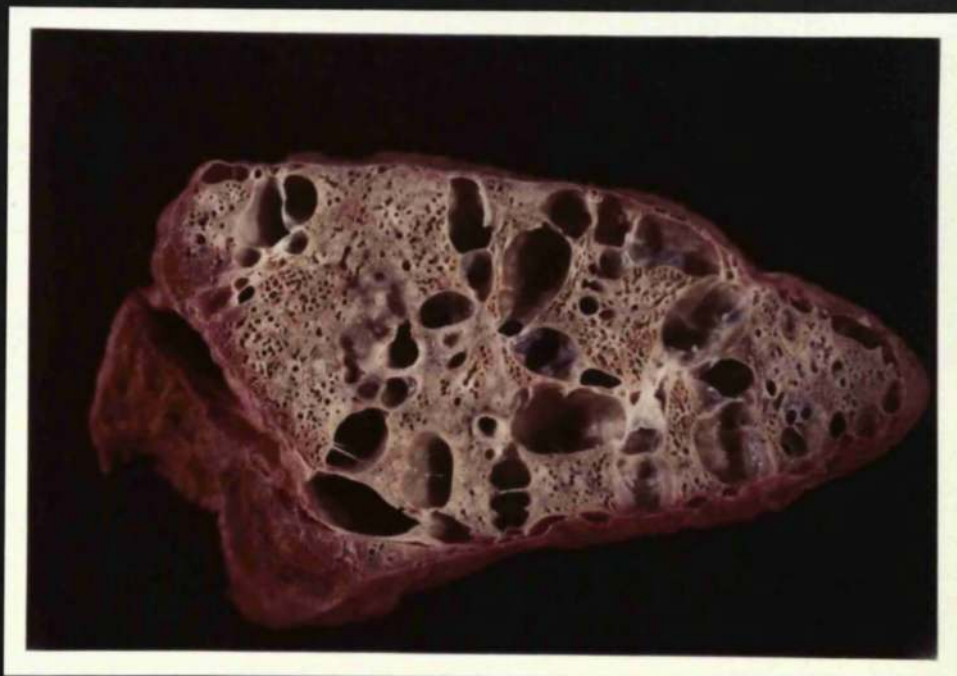
(corrosive-formol fixed lung of fatal case: the pleura is tinged with eosin).

Fig. 17 Fog fever: mediastinal lymph node of :-

non-fatal case (left) is enlarged, congested and oedematous.

fatal case (right) is congested, haemorrhagic, oedematous and contains blood filled gas bullae.

16



17

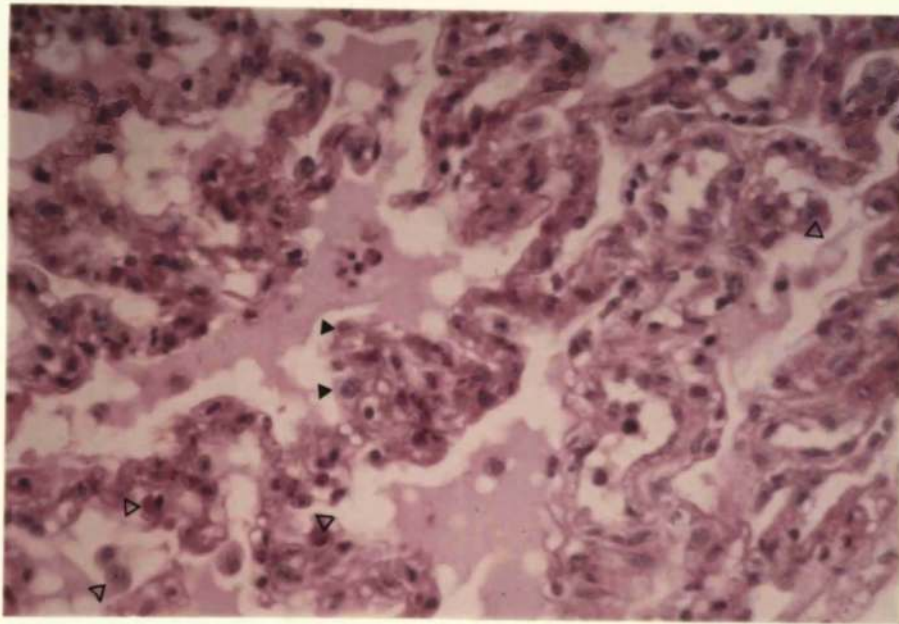


Fig. 18 Fog fever: pulmonary oedema and congestion; P.A.S.

positive granules in type 2 pneumonocytes (arrow) and,
in larger amount, in alveolar macrophages (open arrow).
(lung of fatal case, stained P.A.S., X 250).

Fig. 19 Fog fever: pulmonary oedema with eosinophilic hyaline
membranes in alveoli and alveolar ducts. Early alveolar
epithelial hyperplasia (grade 1+) in some alveoli.
(lung of fatal case, stained H & E, X 110)

18



19

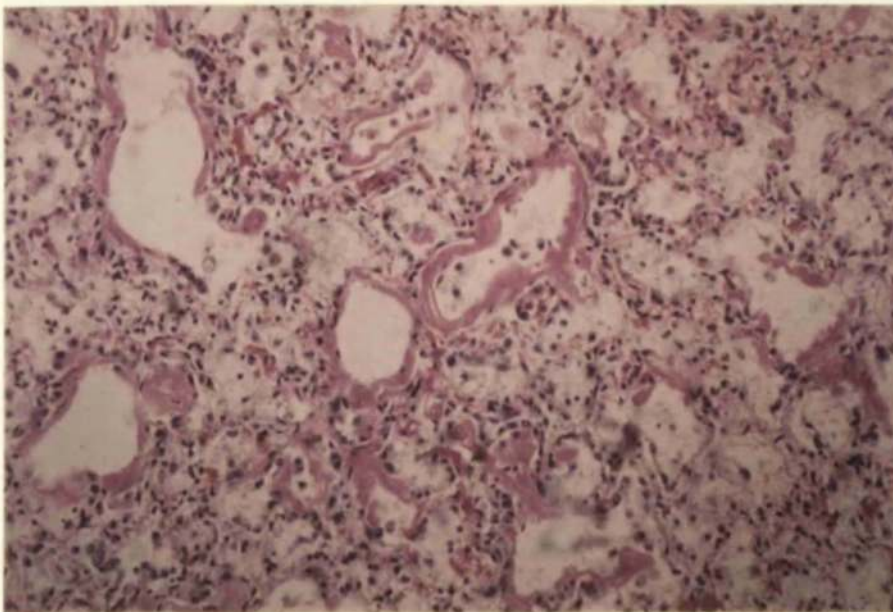


Fig. 20 Fog fever: pulmonary oedema with eosinophilic hyaline
membranes, some of which enmesh large mononuclear cells.
early alveolar epithelial hyperplasia (1+) also,
(lung of fatal case, stained H & E, X 300).

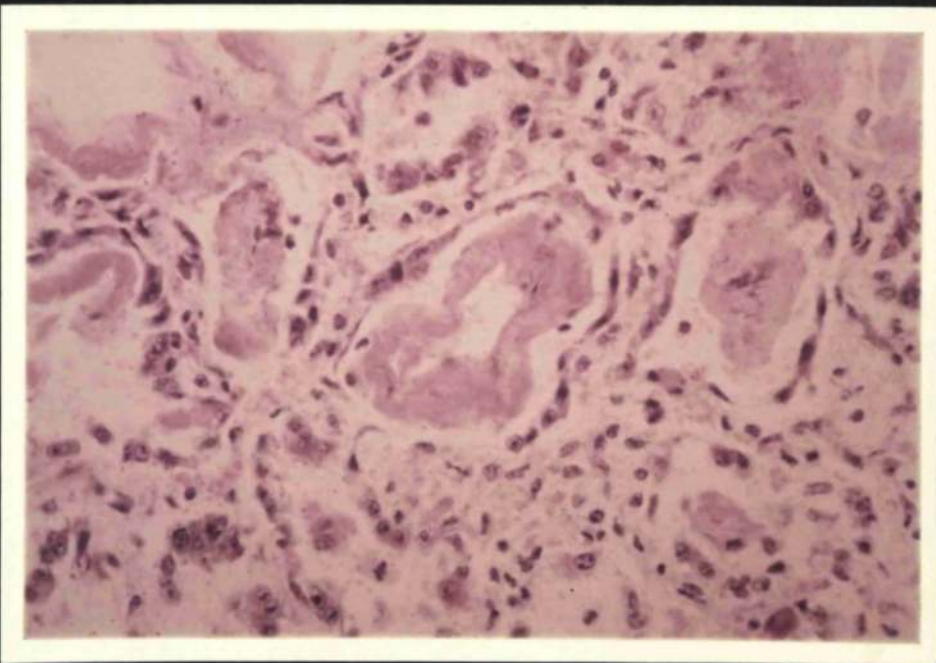


Fig. 21: basophilic hyaline membranes infiltrated by
macrophages and neutrophils in alveolar spaces.
There is alveolar oedema and an exudate of
neutrophils, macrophages and eosinophils.

(H+E, x 350)

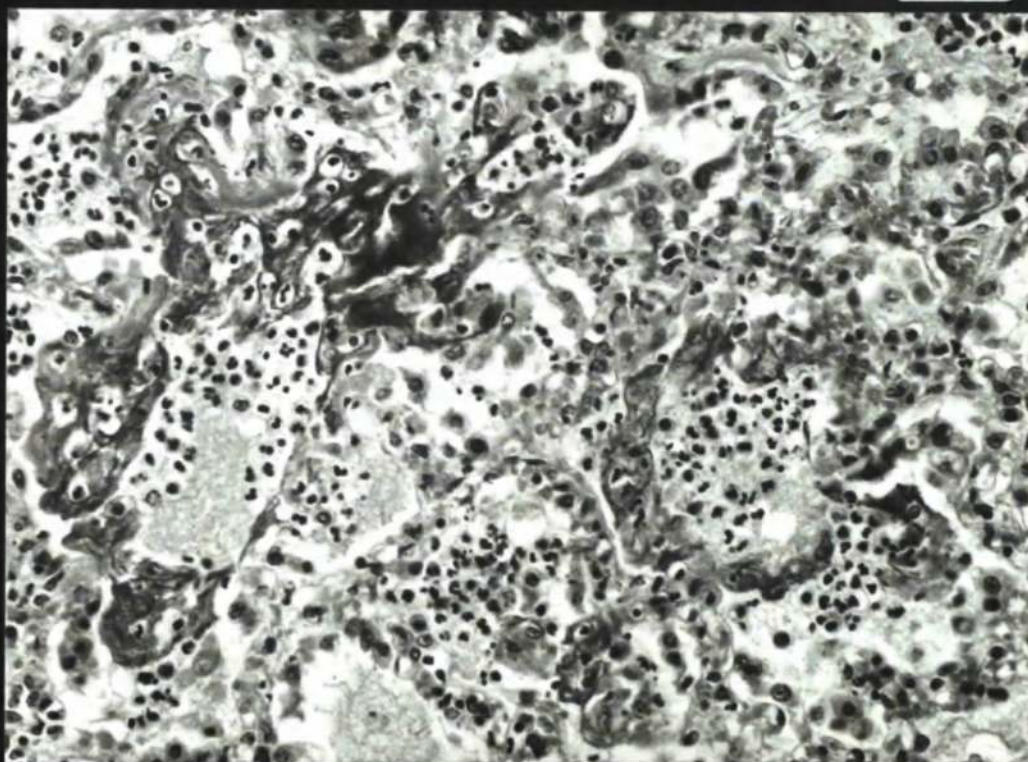
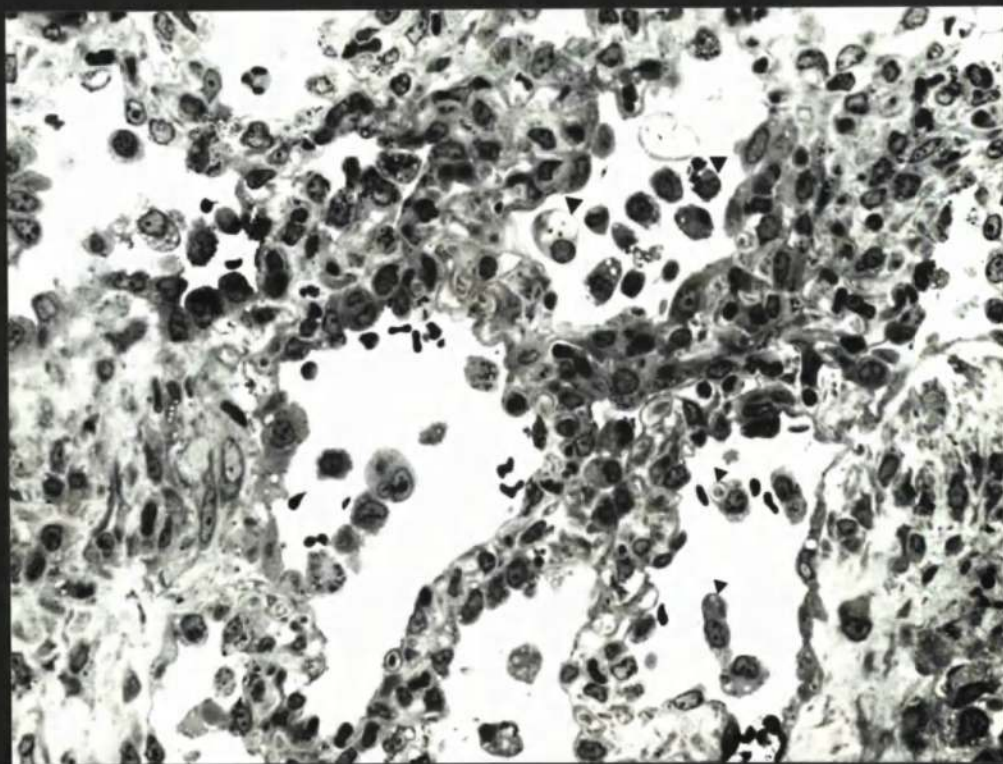


Fig. 22 Fog fever: proliferation of alveolar epithelial cells and pulmonary oedema. Many of the large mononuclear cells in the alveolar spaces are alveolar macrophages, containing phagosomes, vacuolated cytoplasm and indented nuclei (arrows).
(Toluidine blue thick section, x 500).

Fig. 23 Fog fever: proliferation of alveolar epithelial cells with oedema and heavy cellular infiltration of interlobular septum by plasma cells, lymphocytes, eosinophils, neutrophils and macrophages.
(H+E, x 300).

22



23

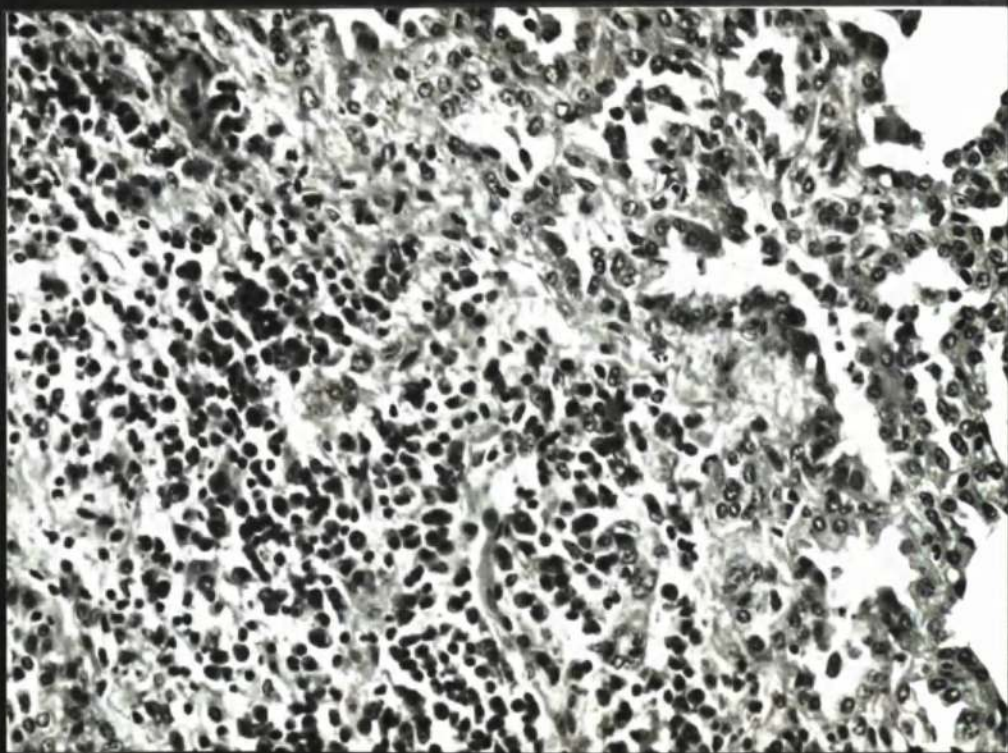
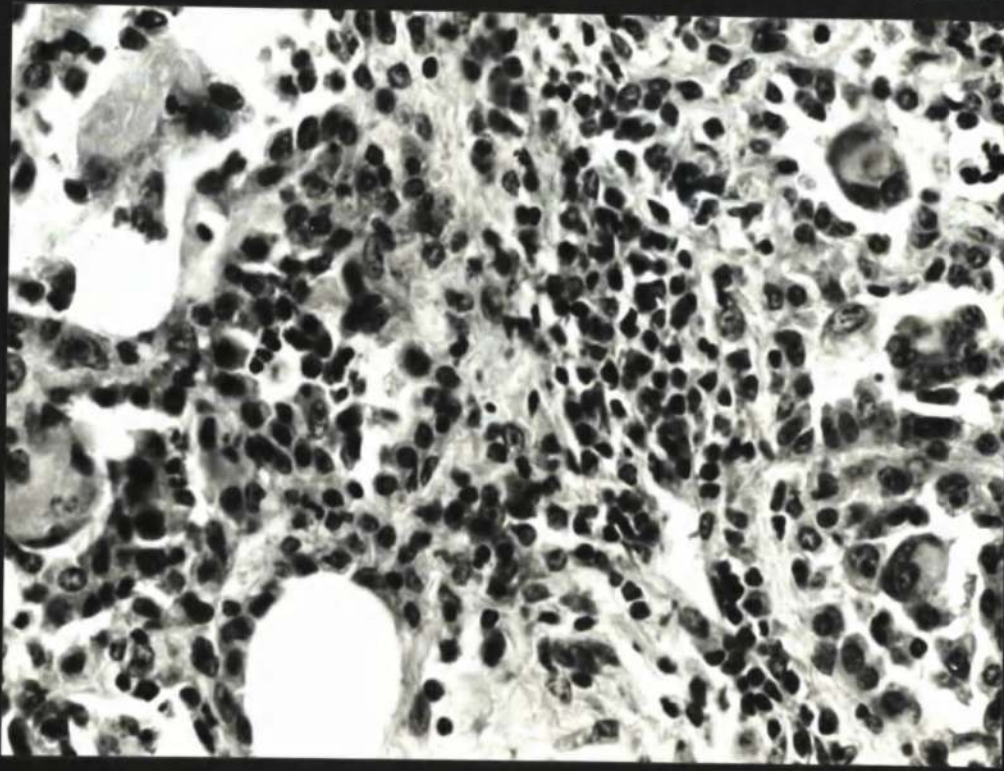


Fig. 24 Fog fever: infiltration of interlobular septum by lymphocytes, plasma cells and eosinophils. Multinucleated giant cells in alveolar spaces.
(H+E, x 500).

Fig. 25 Fog fever: congestion of alveolar septal capillaries and proliferation of alveolar epithelial cells (1+).
(H+E, x 300).

24



25

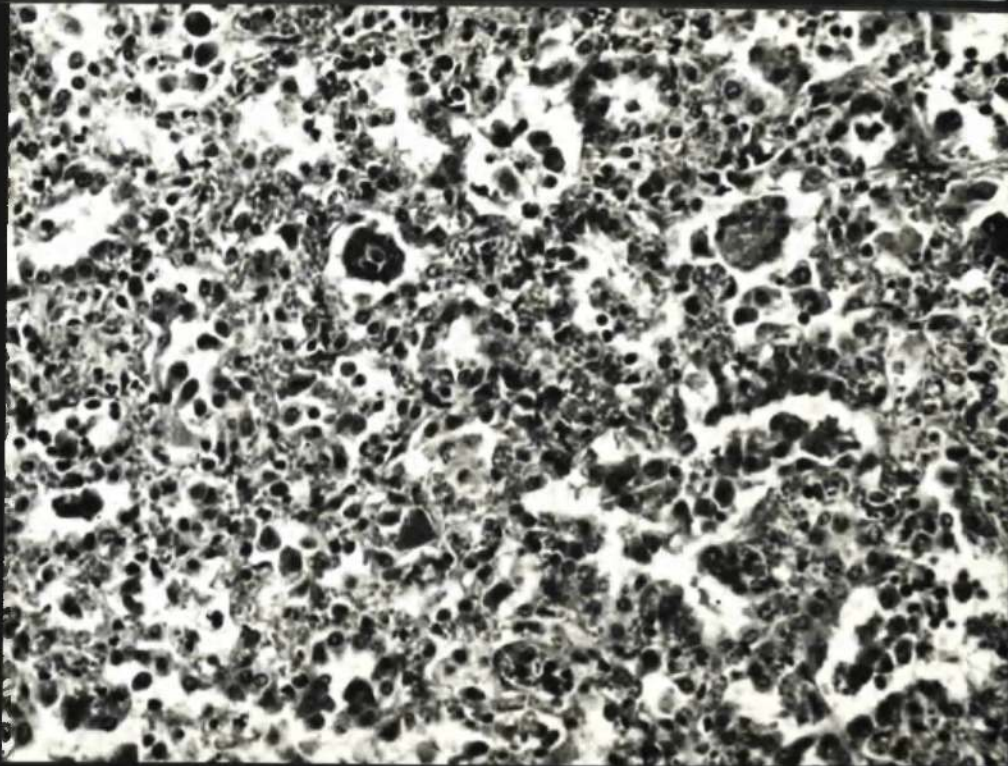


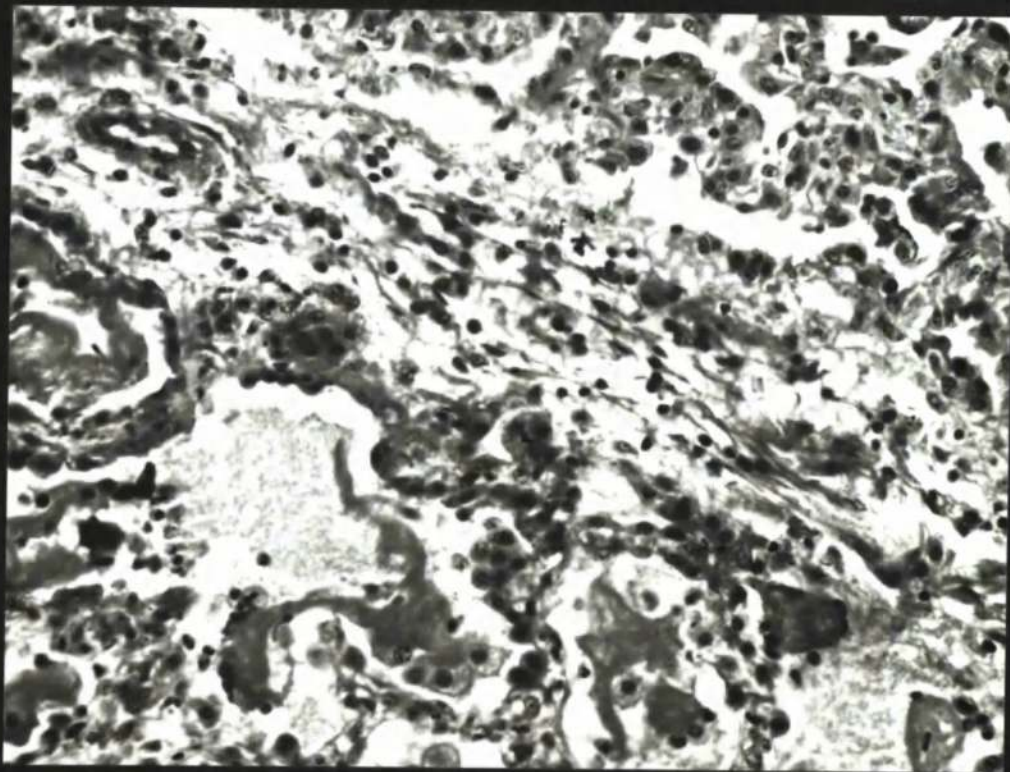
Fig. 26 Fog fever: acini in one lobule (top right) are empty and there is early proliferation of alveolar epithelial cells. The interlobular septum is oedematous. Acini in adjacent lobule (lower left) are filled by oedema fluid and hyaline membranes with large mononuclear cells; there is also more extensive proliferation of alveolar epithelial cells.

(H+E, x 300)

Fig. 27 Fog fever: overinflation of acini in one lobule and overinflation with oedema, hyaline membranes and alveolar epithelial hyperplasia in an adjacent lobule.

(H+E, x 50)

26



27

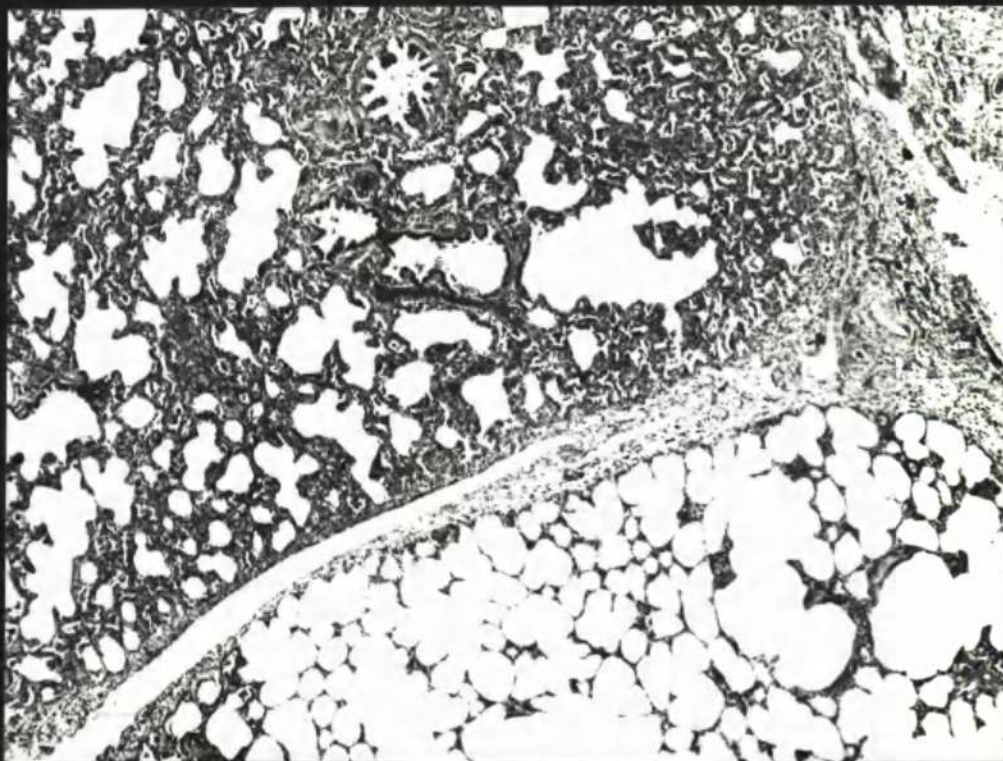
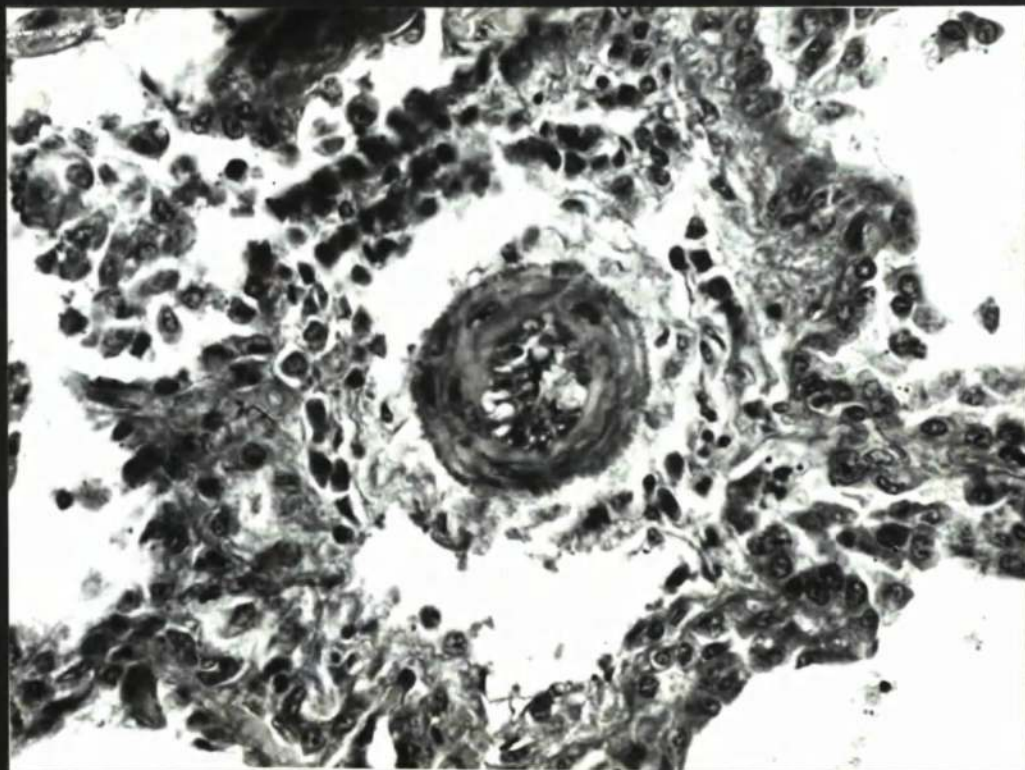


Fig. 28 Fog fever: perivascular oedema and gas infiltration
with oedema fluid below the endothelium of a venule.
(H+E, x 500)

Fig. 29 Fog fever: subendothelial oedema and loss of
staining affinity of a portion of the media of
a venule.
(H+E, x 300)



29

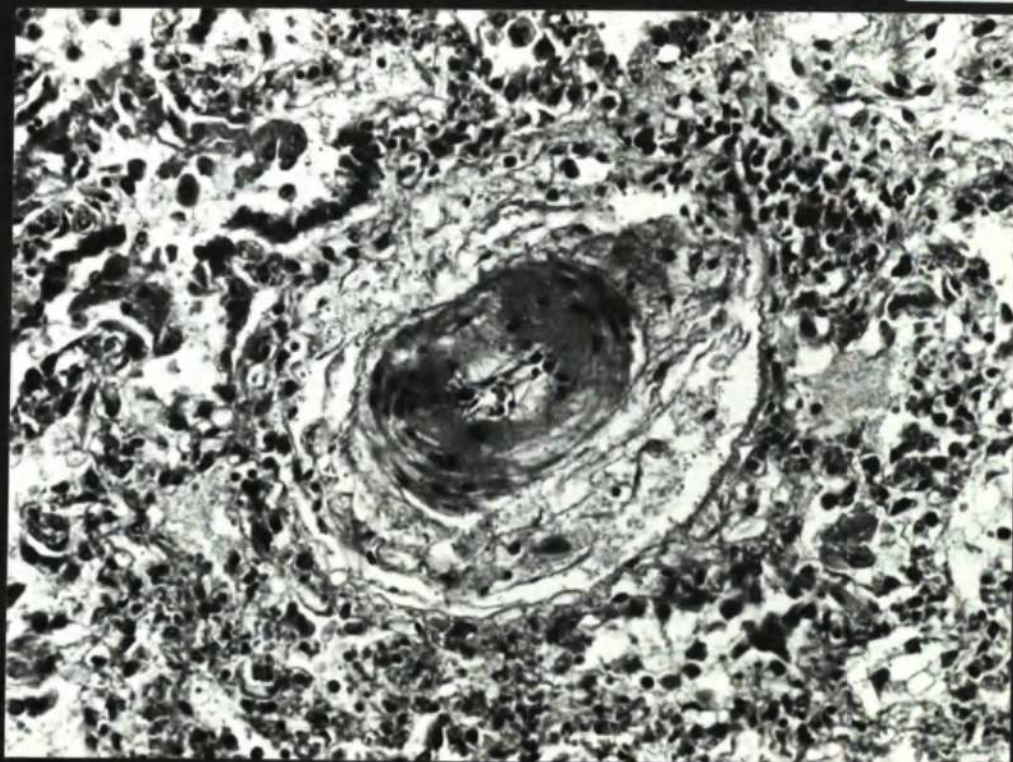


Fig. 30 Fog fever: diffuse alveolar epithelial hyperplasia affecting all lung lobes, there are a few normal lobules in the cardiac lobe.

Fig. 31 Fog fever: cross section of diaphragmatic lobe of lung illustrated in Fig. 30 . Note diffuse alveolar epithelial hyperplasia; large interstitial gas bulla; perivascular and peribronchial tracking of gas.

30



31



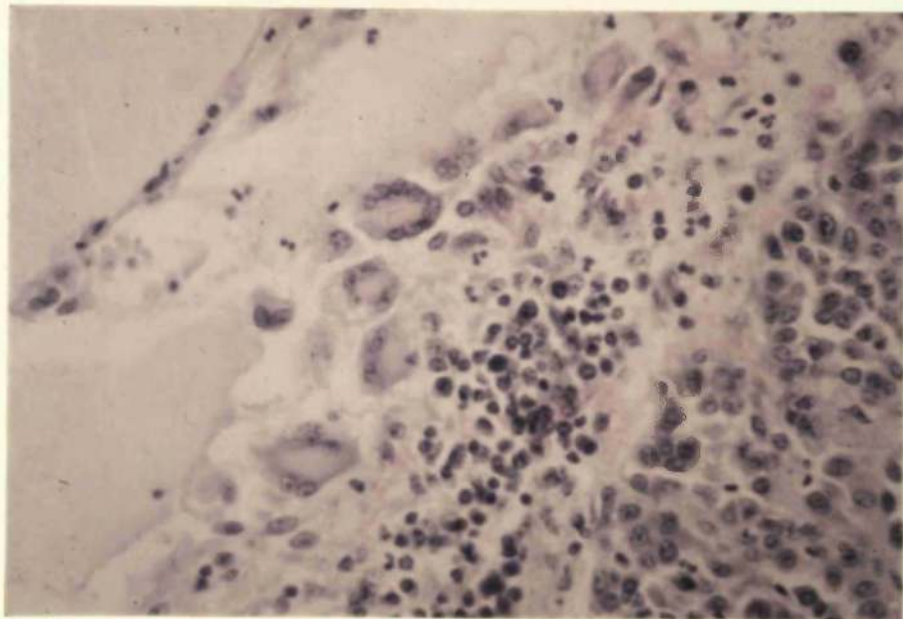
Fig. 32 Fog fever: multinucleated giant cells in interlobular
septa.

(Carbol chromotrope, X 500)

Fig. 33 Fog fever: globule leucocytes between bronchial
epithelial cells; there is also oedema and plasma
cell and lymphocyte infiltration of the lamina
propria.

(non-fatal case, H & E, X 500)

32



33

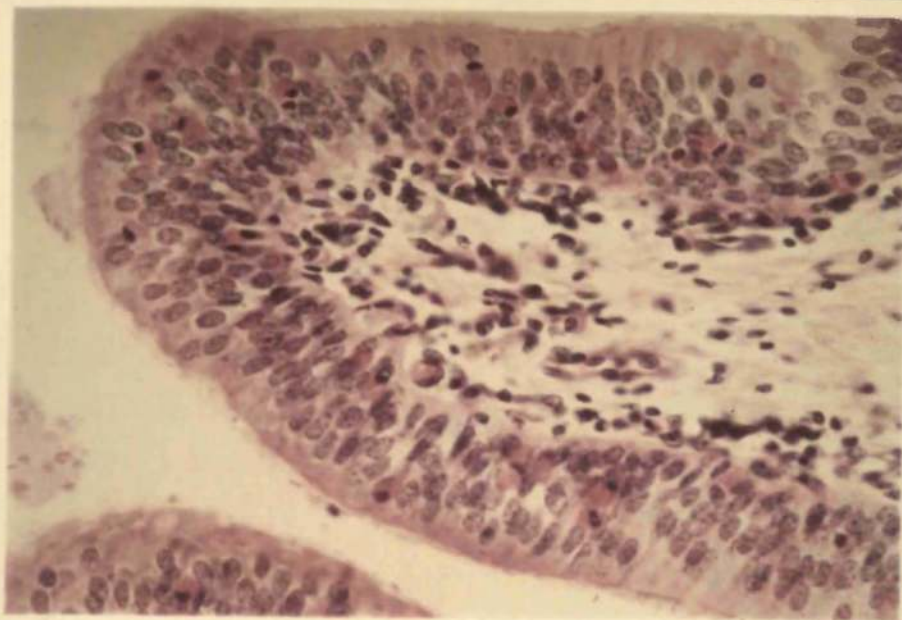
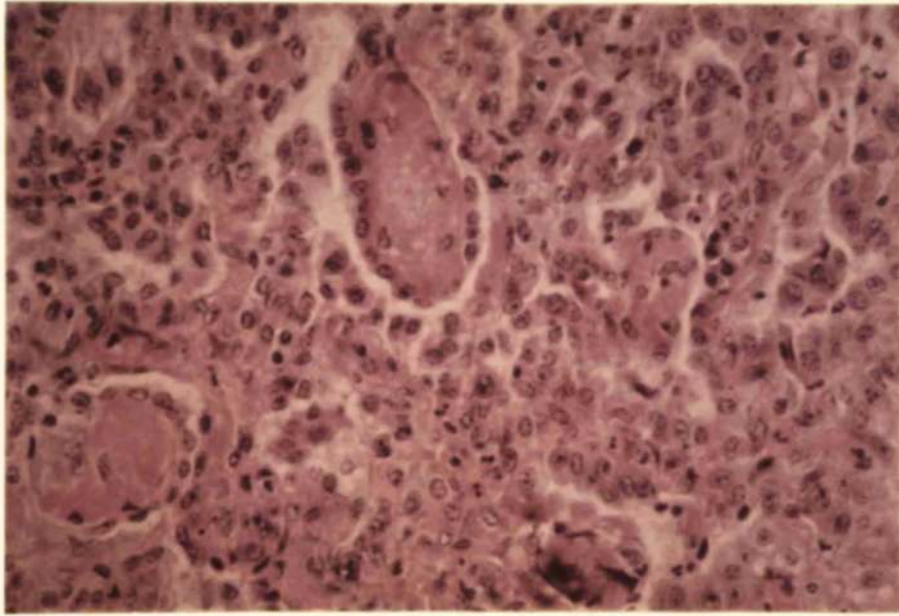


Fig. 34 Fog fever: eosinophilic hyaline material in
alveolar spaces is infiltrated by macrophages.
Some of the hyaline material is basophilic.
(H+E, x 300).

Fig. 35 Fog fever: extreme alveolar epithelial hyperplasia.
(P.A.S., x 450).

34



35

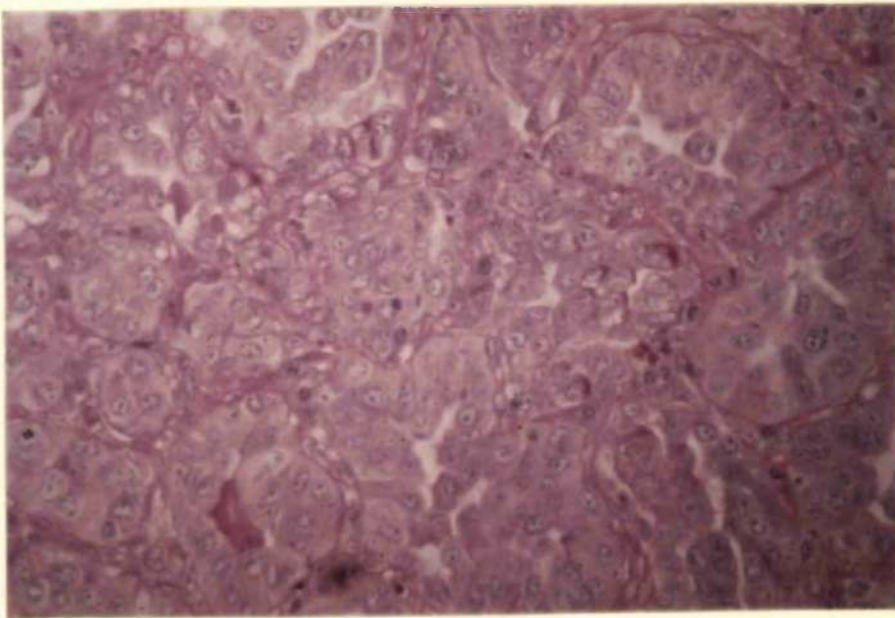


Fig. 36 . Fog fever: oedema of alveolar septa with occasional

fine collagen strands. Resolving intra-alveolar

Fig.

exudate also.

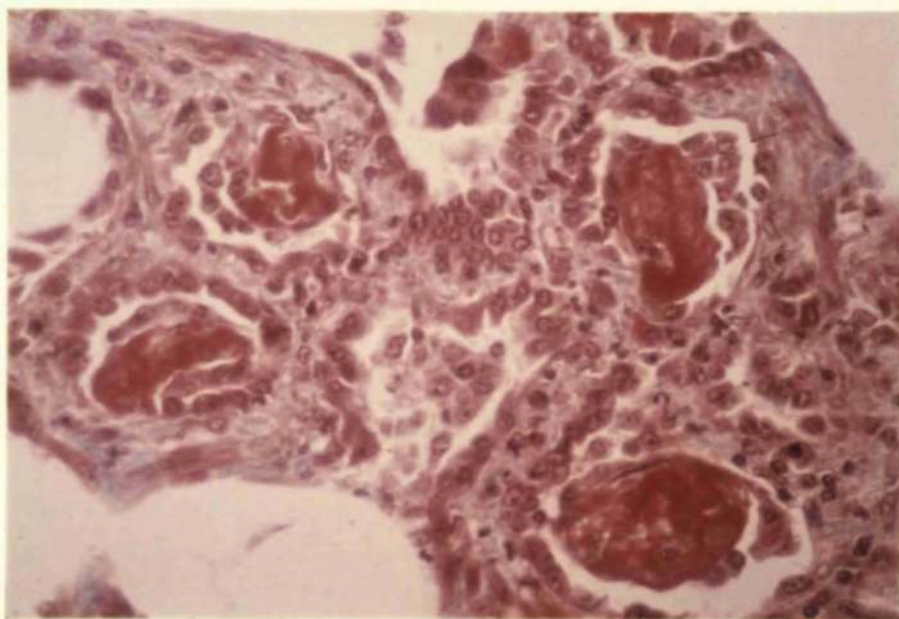
(picro-Mallory, x 400).

Fig. 37 Fog fever: incorporation of intra-alveolar exudate

into alveolar wall.

(picro-Mallory, x 400).

36



37

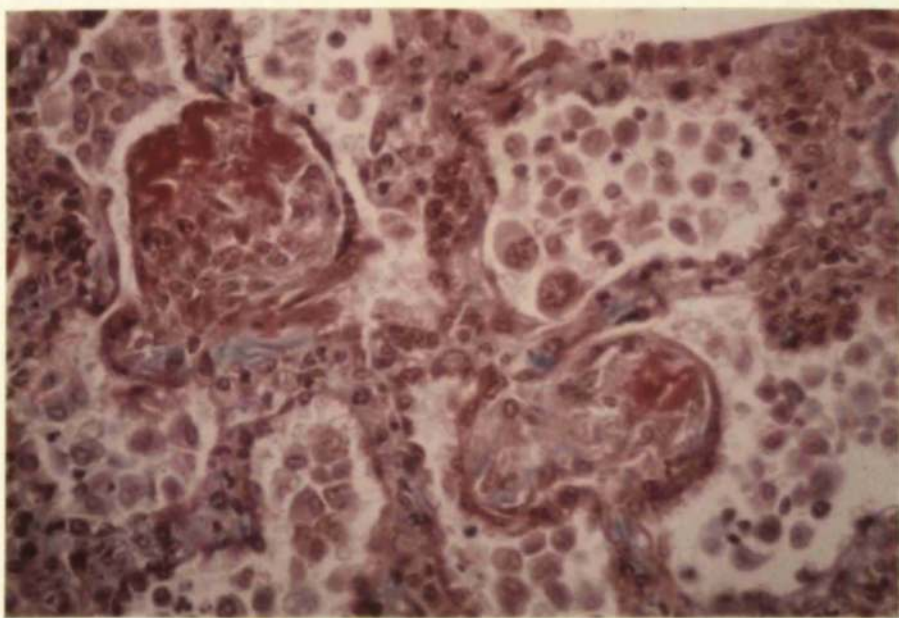


Fig. 38 Fog fever: oedema of alveolar septa and diffuse
alveolar epithelial hyperplasia.

(H+E, x 50)

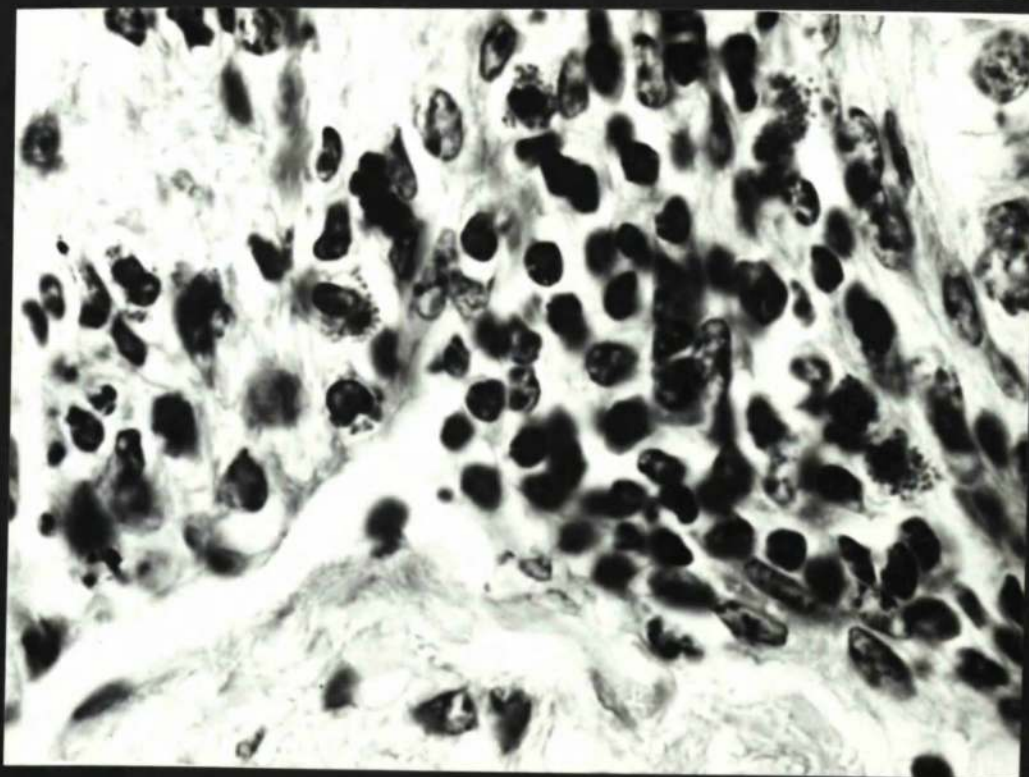
Fig. 39 Fog fever: eosinophils in perivascular connective
tissue.

(H+E, x 1200)

38



39



470

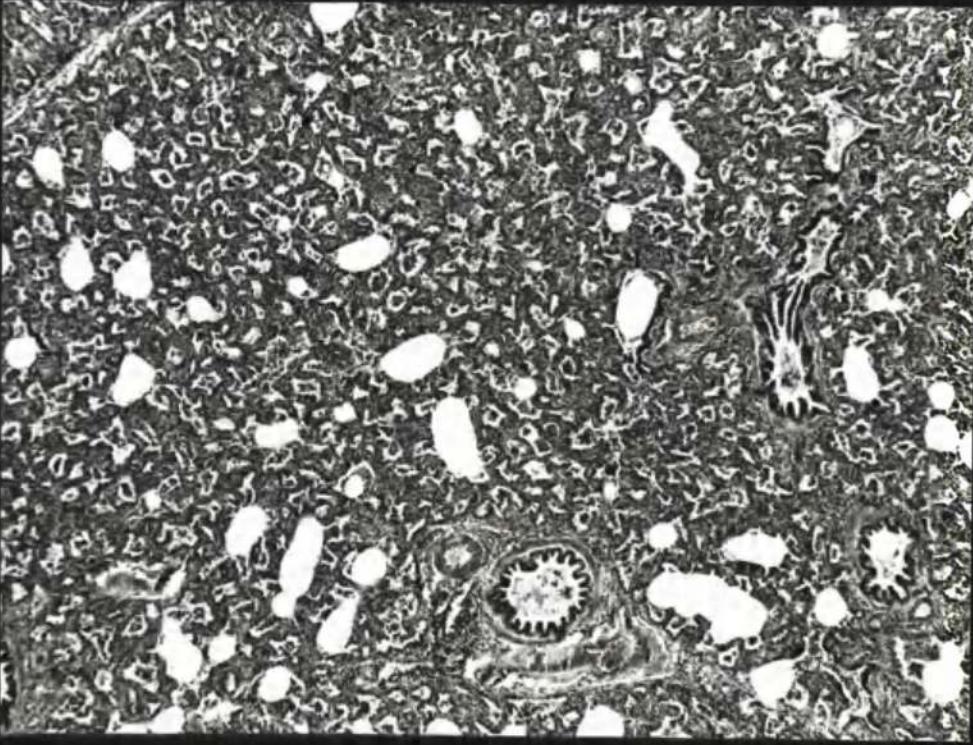
Fig. 40 Fog fever: alveolar epithelial hyperplasia involving
all the acini in the lobule.

(H+E, x 50)

Fig. 41 Fog fever: alveolar epithelial hyperplasia with
accumulation of large mononuclear cells in the
alveolar spaces.

(H+E, x 500)

40



41

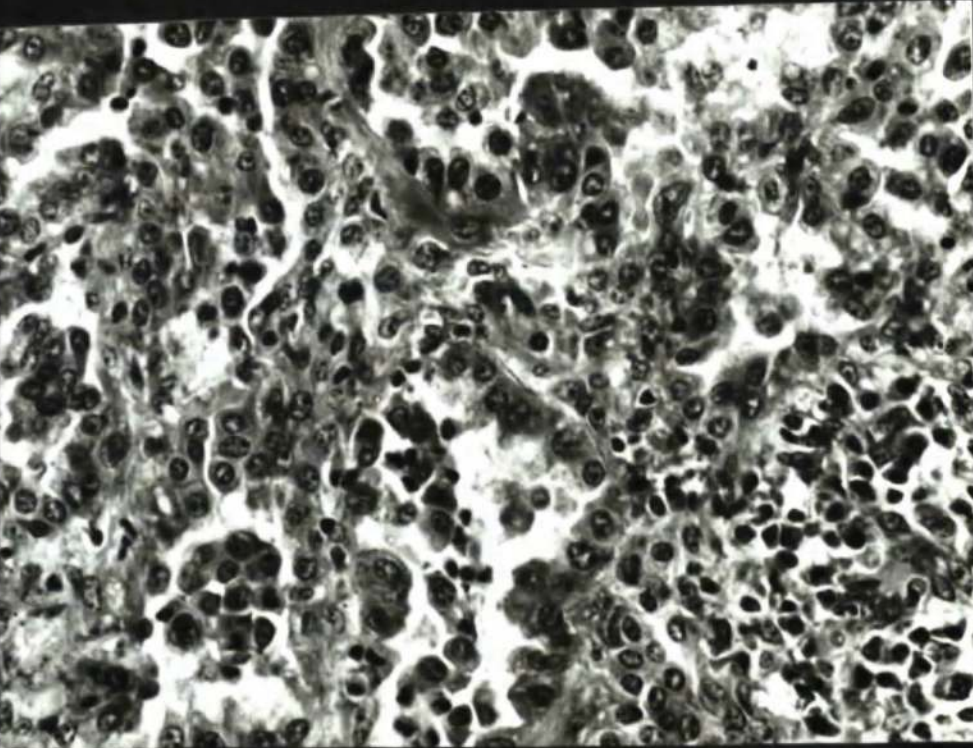
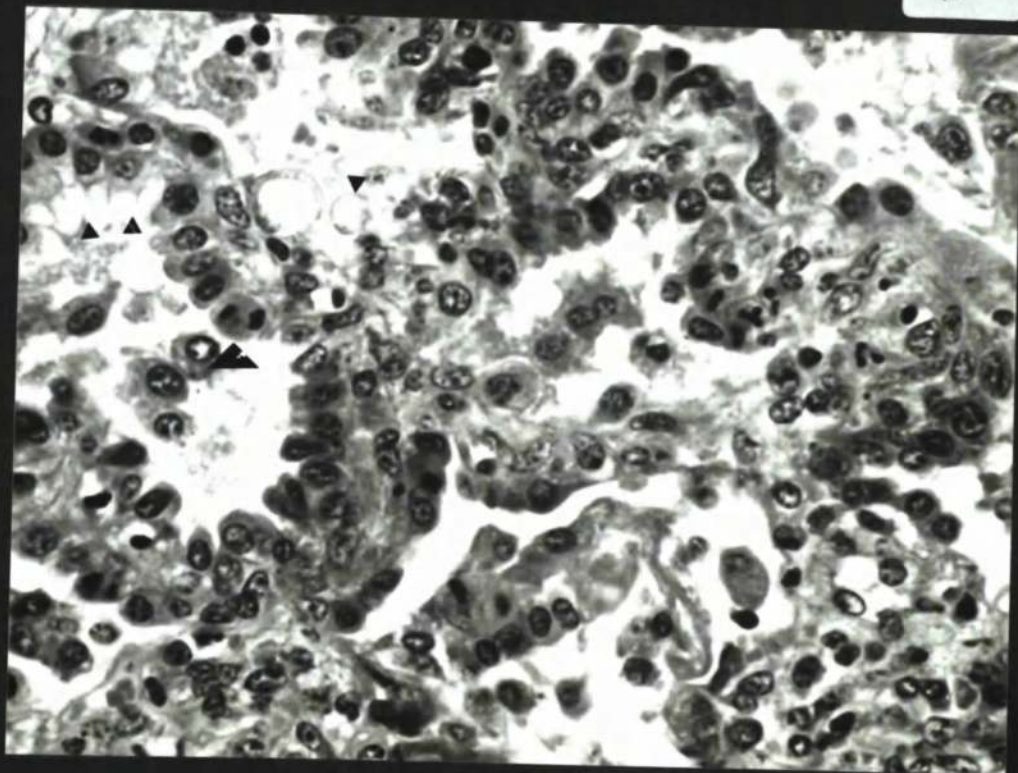


Fig. 42 Fog fever: large mononuclear cells in alveolar spaces. Mitosis in alveolar epithelial lining cells (large arrow). Vacuolated, apical 'cap' of epithelial cells and round cytoplasmic bodies in alveolar spaces (small arrows).
(H+E, x 500).

Fig. 43 Fog fever: thickening and oedema of alveolar septa with numerous interstitial cells (arrow) and some neutrophils and eosinophils.
(H+E, x 300).

42



43

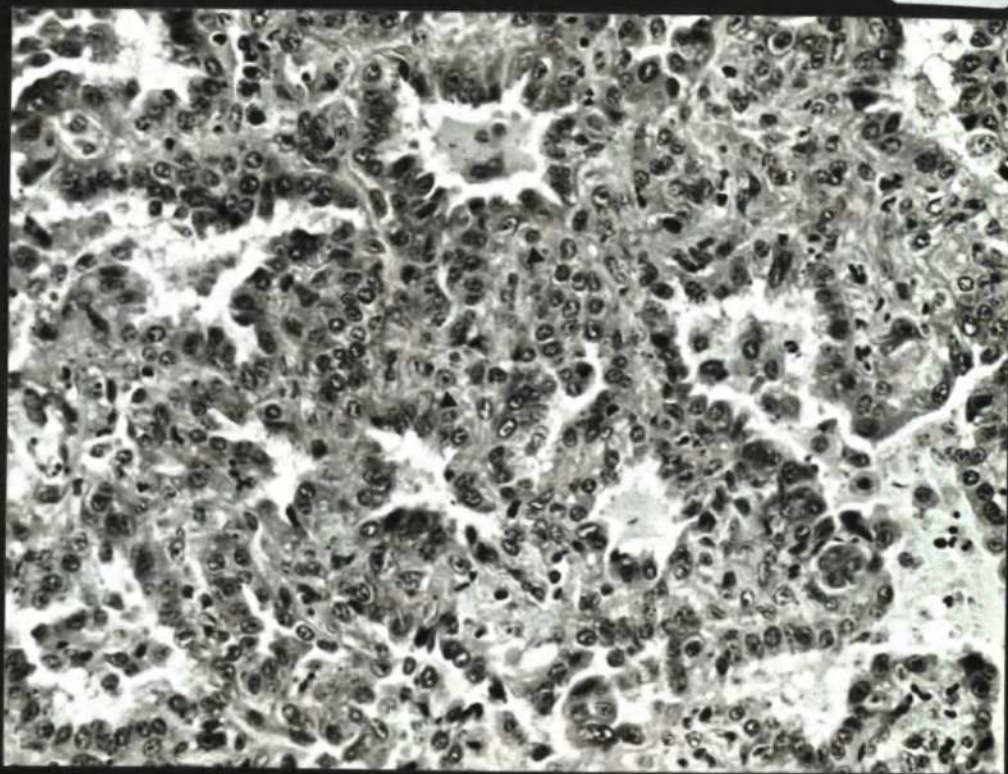


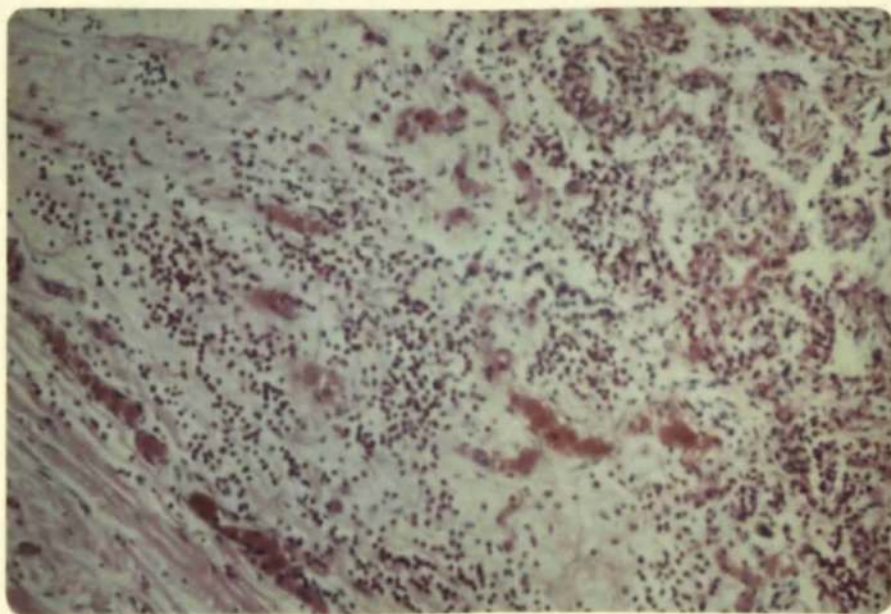
Fig. 44 Fog fever: eosinophils in peribronchiolar connective
tissue, alveolar septa and alveoli.

(H+E, x 40)

Fig. 45 Fog fever: detail of Fig. (44) - eosinophils.

(H+E, x 300)

44



45

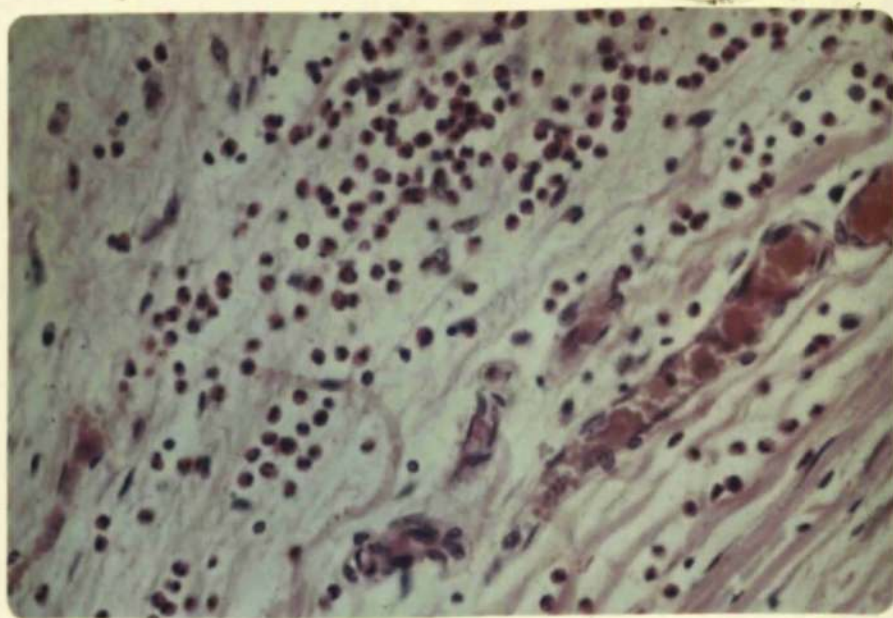


Fig. 46 Diffuse fibrosing alveolitis: reddish brown, fibrous pleural tags particularly on diaphragmatic lobes and a few grey-red collapsed lobules (arrow).

Fig. 47 Diffuse fibrosing alveolitis: pale pink lungs with small grey spots in some lobules.

46



47

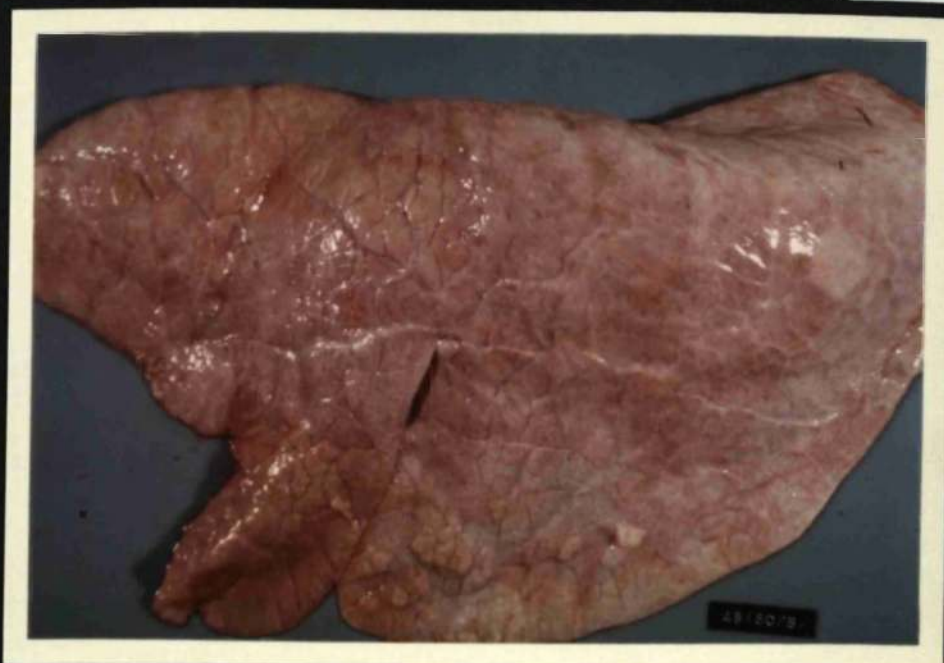


Fig. 48 Diffuse fibrosing alveolitis: most lung lobules are pale pink or white but a few are greyish-red, collapsed and oedematous.

Fig. 49 Diffuse fibrosing alveolitis: pale, fleshy, non-spongy lung in which there is alveolar epithelial hyperplasia and cellular infiltration of alveolar septa.

48



49

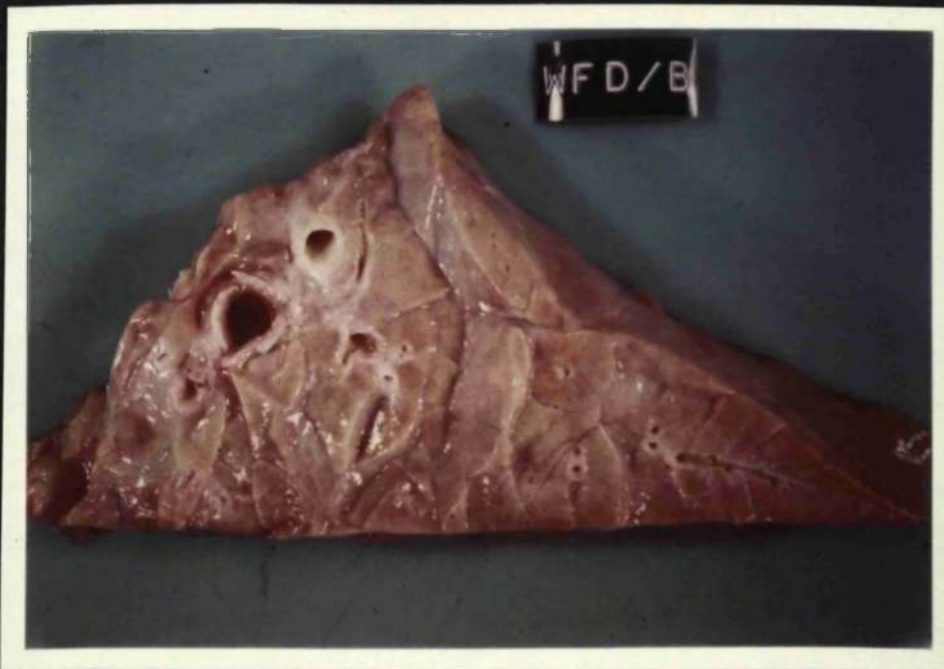


Fig. 50 Diffuse fibrosing alveolitis: white, fleshy lobules affected by this disease (left) contrast with spongy, pink tissue (right) from normal animal.

Fig. 51 Diffuse fibrosing alveolitis: lobules have lost their normal spongy texture and have grey, solid parts. Grey tissue band is apparent about the bronchioles.
(formalin fixed specimen).

50



51



Fig. 52 Diffuse fibrosing alveolitis: thick tenacious mucus strands in trachea.

Fig. 53 Diffuse fibrosing alveolitis: thick mucus lying in lobar and segmental bronchi. Grey-red collapsed lobules can be seen in the lung (top right and bottom left) and other lobules are pale yellow in colour.

52



53



Fig. 54 Diffuse fibrosing alveolitis: bronchiolar lumen filled by macrophages and neutrophils. Alveolar epithelial hyperplasia and accumulation of large mononuclear cells and neutrophils in alveolar spaces. Alveolar septa heavily infiltrated by lymphocytes and plasma cells.

(H+E, x 110)

Fig. 55 Diffuse fibrosing alveolitis: accumulation of large mononuclear cells with oedema fluid in alveolar spaces. Diffuse alveolar septal fibrosis and cellular infiltration by lymphocytes and plasma cells.

(H+E, x 50)

54



55

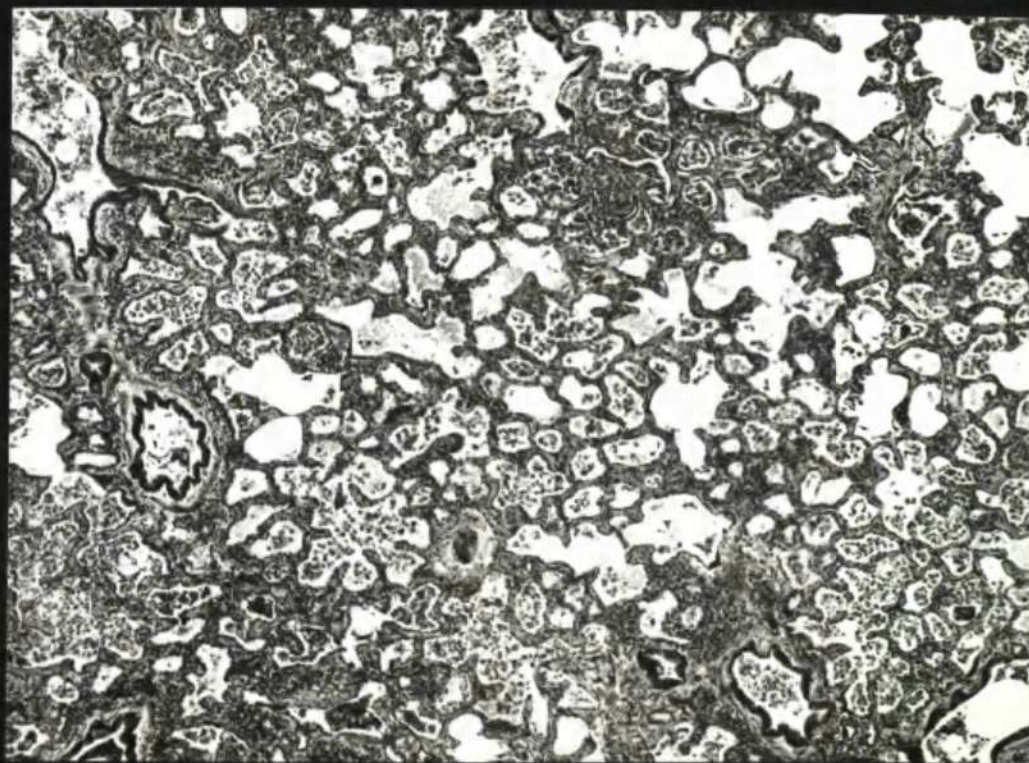


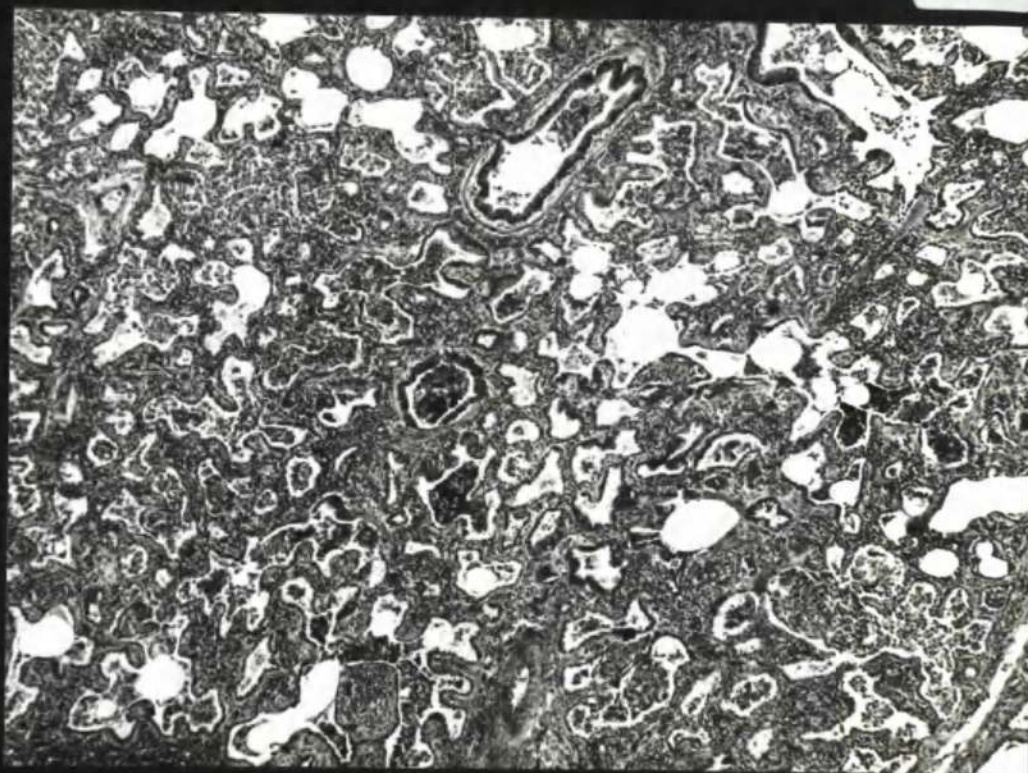
Fig. 56 Diffuse fibrosing alveolitis: widespread changes throughout the lobule. There is alveolar epithelial hyperplasia; accumulation of large mononuclear cells in alveolar spaces; fibrosis and infiltration of plasma cells and lymphocytes in the alveolar septa; a mixture of basophilic hyaline material and macrophages in the bronchioles.

(H+E, x 50)

Fig. 57 Diffuse fibrosing alveolitis: alveolar epithelial hyperplasia in most lobules with discrete cells on some alveolar walls and a focus of tall columnar, ciliated cells (arrow).

(H+E, x 300)

56



57

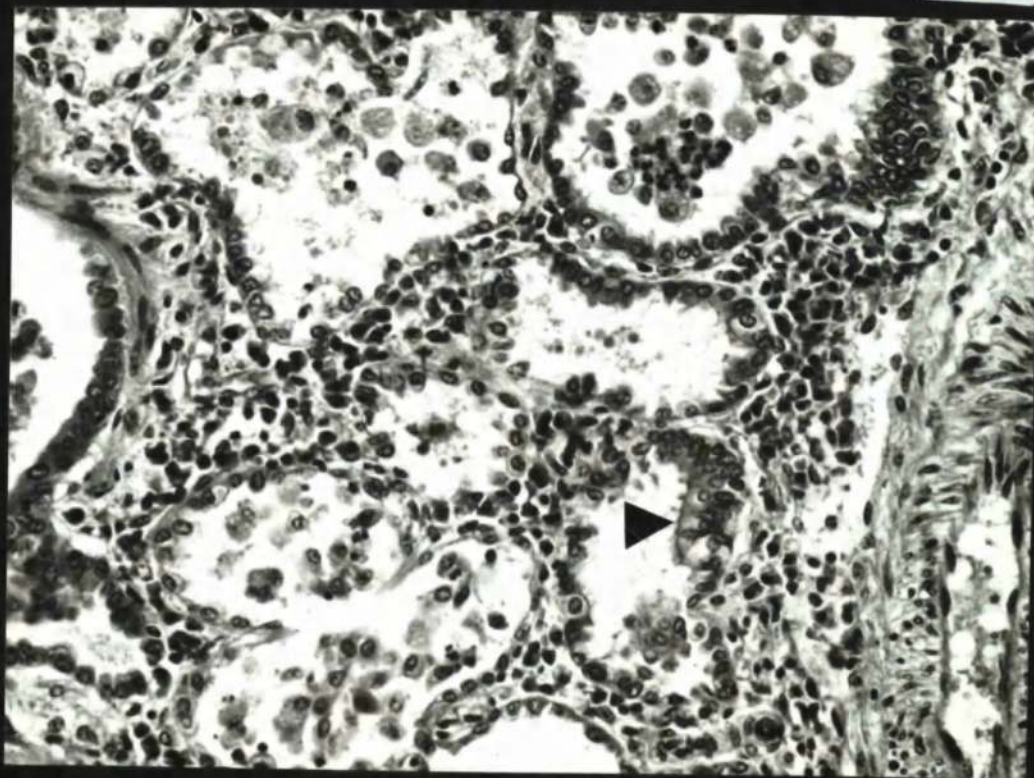


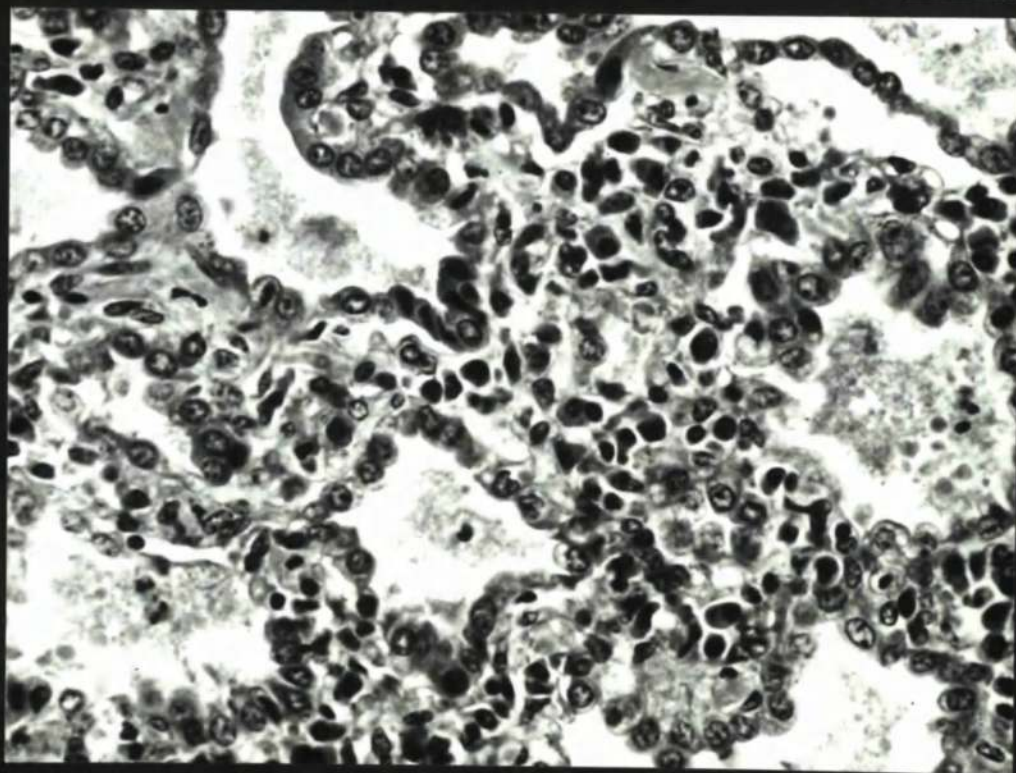
Fig. 58 Diffuse fibrosing alveolitis: lymphocytes, plasma cells and interstitial cells in alveolar septa. There is also alveolar epithelial hyperplasia and oedema.

(H+E, x 500)

Fig. 59 Diffuse fibrosing alveolitis: distortion and obliteration of alveoli by fibrosis and cellular infiltration of alveolar septa.

(H+E, x 110)

58



59



Fig. 60 Diffuse fibrosing alveolitis: one or more layers of

cuboidal cells form the alveolar epithelium; similar large, mononuclear cells predominate in the lumen. The alveolar interstitium is greatly thickened by fibrosis and cellular infiltration, principally by plasma cells and lymphocytes with mast cells.

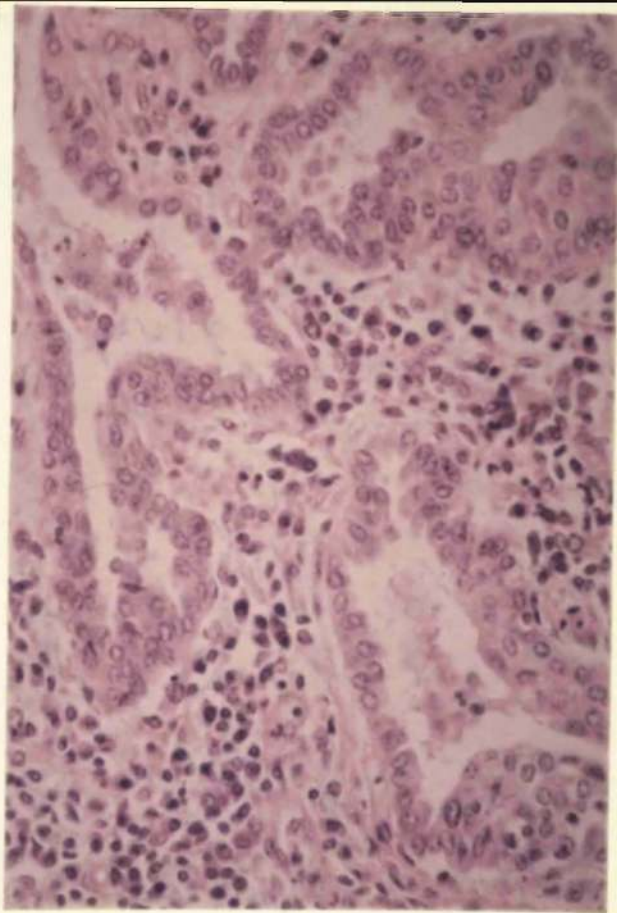
(H & E, X 500)

Fig. 61 Diffuse fibrosing alveolitis: the alveoli are lined by

tall columnar ciliated cells resembling bronchiolar epithelium. Marked plasma cell and lymphocyte infiltration of alveolar septa.

(H & E, X 500)

60



61

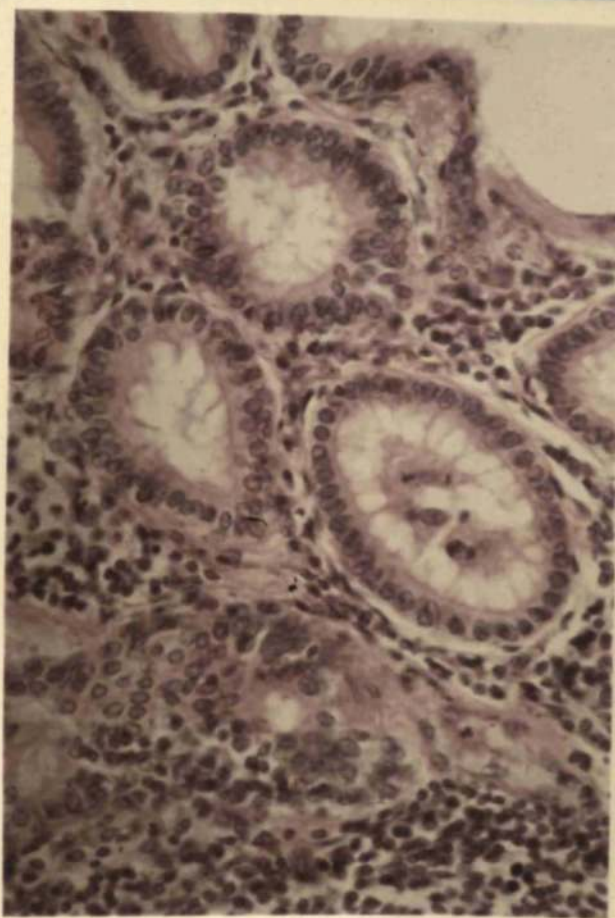
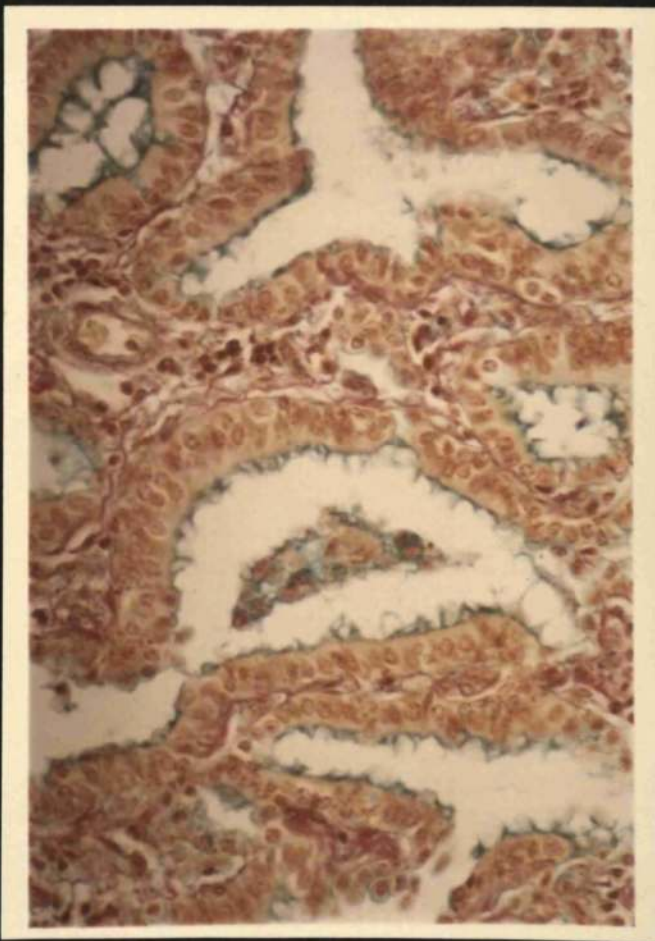


Fig. 62 Diffuse fibrosing alveolitis: alveoli are lined by
tall columnar cells, many of which are ciliated.
(Rinehart - Abu'l Haj, X 500)



63



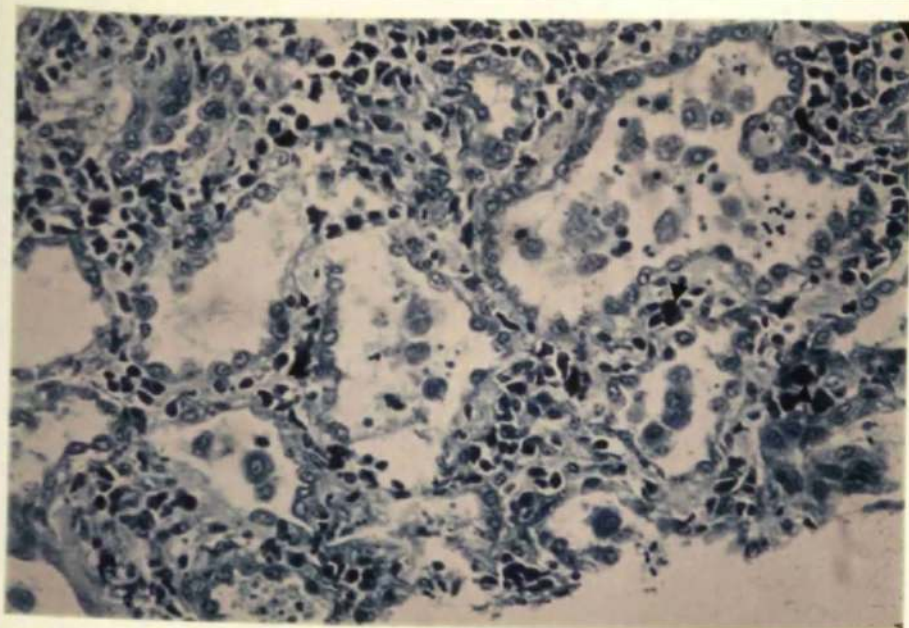
Fig. 64 Diffuse fibrosing alveolitis: mast cells in alveolar septa (arrows).

(toluidine blue, X 300)

Fig. 65 Diffuse fibrosing alveolitis: increased reticulin in alveolar septa.

(Gordon and Sweet, X 500)

64



65



Fig. 66 Diffuse fibrosing alveolitis: heavy fibrosis of interlobular septa between lobules which are fibrosed and oedematous.

Fig. 67 Diffuse fibrosing alveolitis: mediastinal lymph node from case (E), there is oedema, congestion and haemorrhage, particularly into gas bullae.

66



67

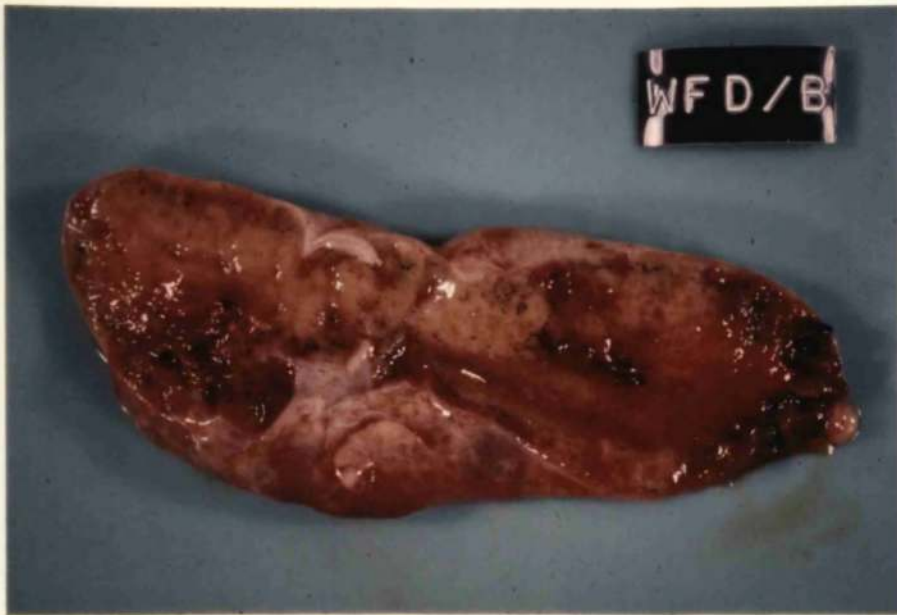
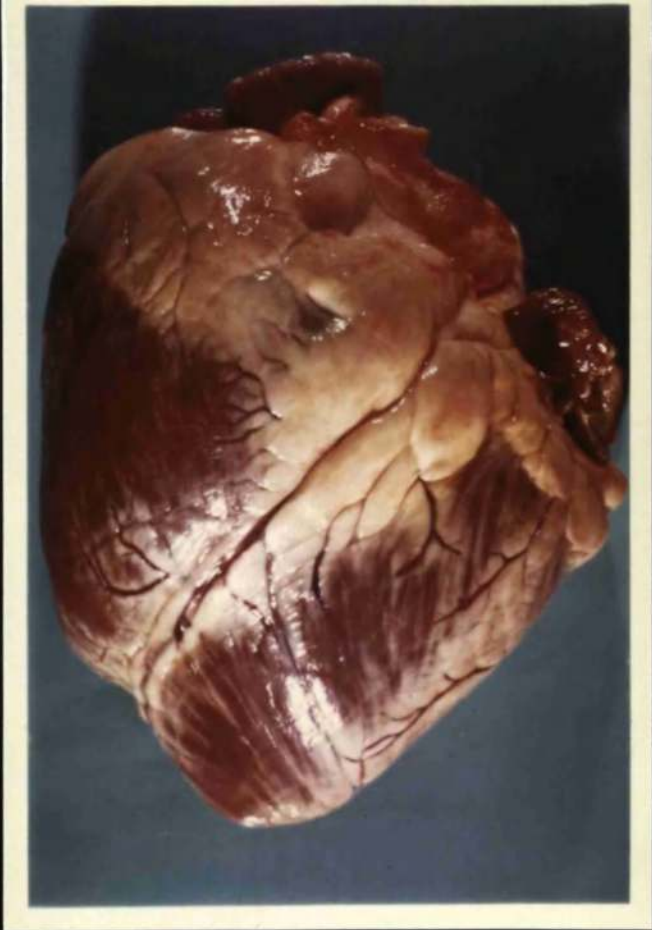


Fig. 68 Diffuse fibrosing alveolitis: enlarged right ventricle
in cor pulmonale.

Fig. 69 Diffuse fibrosing alveolitis: thickened right ventricular
muscle in cor pulmonale.

68



69



Fig. 70 Diffuse fibrosing alveolitis: cor pulmonale with
enlarged pulmonary arterial trunk (PA), which is wider
than the aorta (A).

70

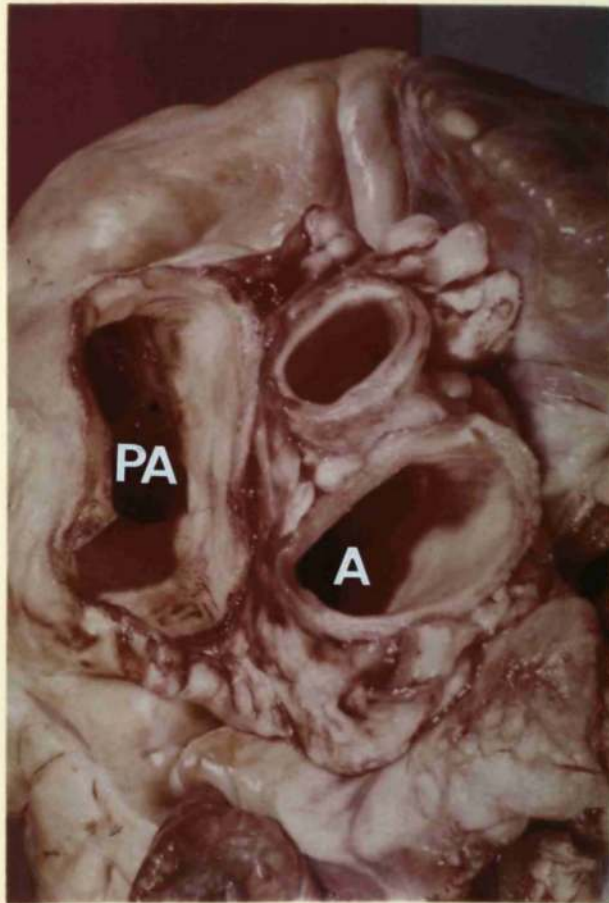


Fig. 71 Bovine farmer's lung: lungs appear relatively normal apart from overinflation of some lobules in anterior lobes.

Fig. 72 Bovine farmer's lung: closer view of apical lobe of lung in Fig. 71 . Small grey spots (arrow) in many lobules with overinflation of peripheral acini which are pale white or pink and raised.

71



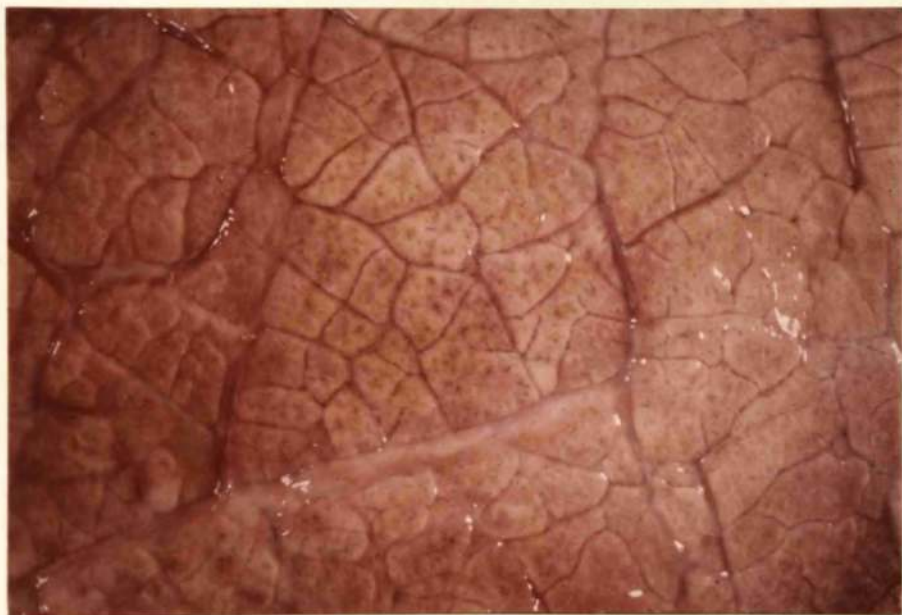
72



Fig. 73 Bovine farmer's lung: small grey spots in the lung lobules with overinflation of the peripheral acini, which appear pale pink and puffy.

Fig. 74 Bovine farmer's lung: small grey spots and peripheral overinflation in most lung lobules; other lobules are white-yellow in colour (centre). This cow also had anthracosis.

73



74

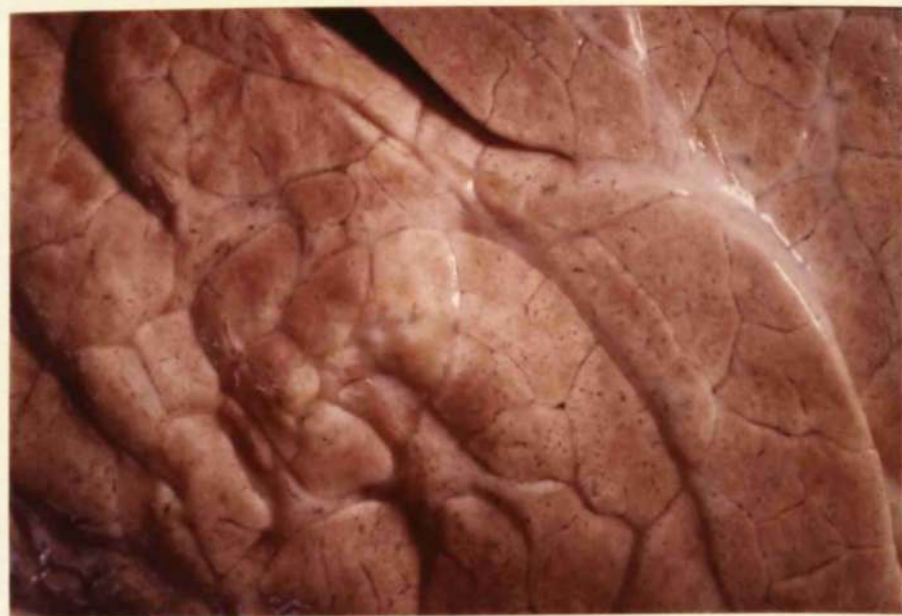


Fig. 75 Extrinsic allergic alveolitis:

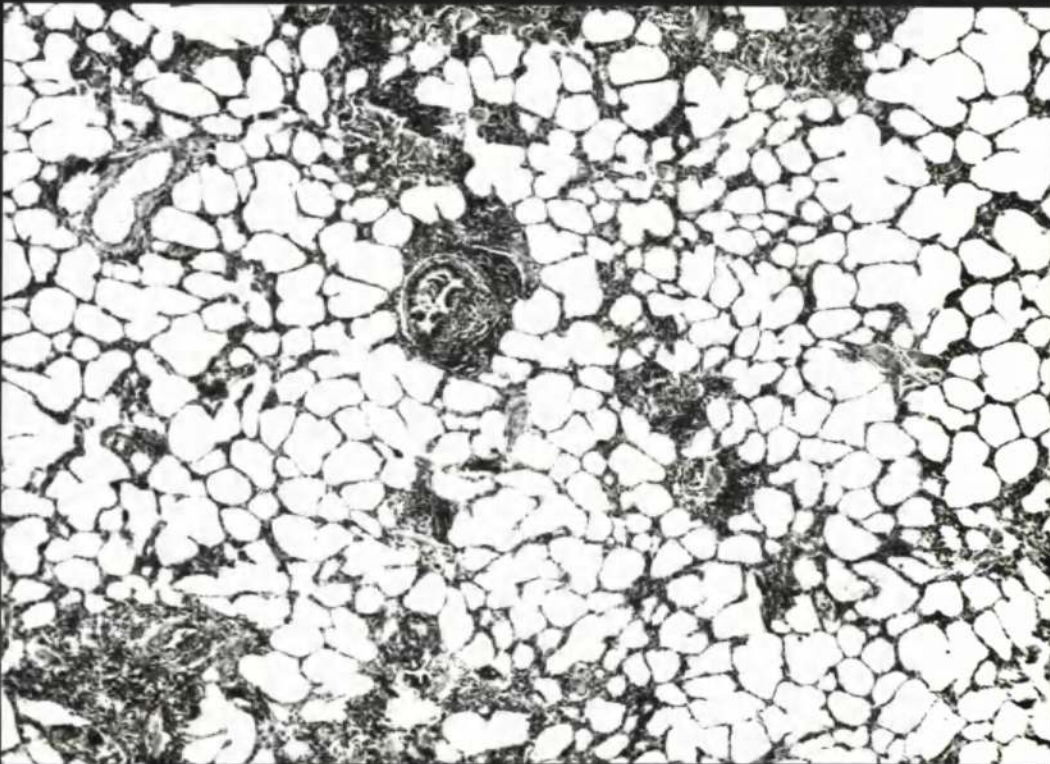
bronchiolitis obliterans with overinflation of respiratory acini and diffuse infiltration of alveolar walls by plasma cells and lymphocytes.

(H & E, x 110)

Fig. 76 Extrinsic allergic alveolitis: diffuse infiltration of alveolar walls by plasma cells and lymphocytes, forming aggregates. Epithelioid granulomata (left corner) with multinucleated giant cell.

(H & E, x 110)

75



76

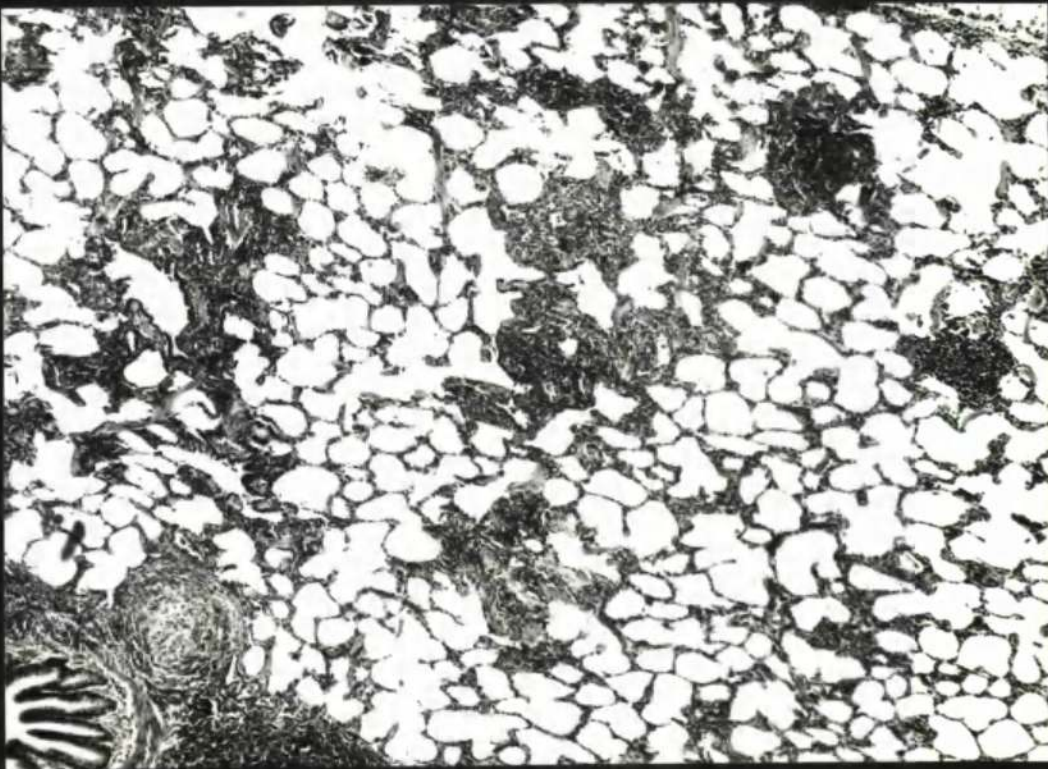


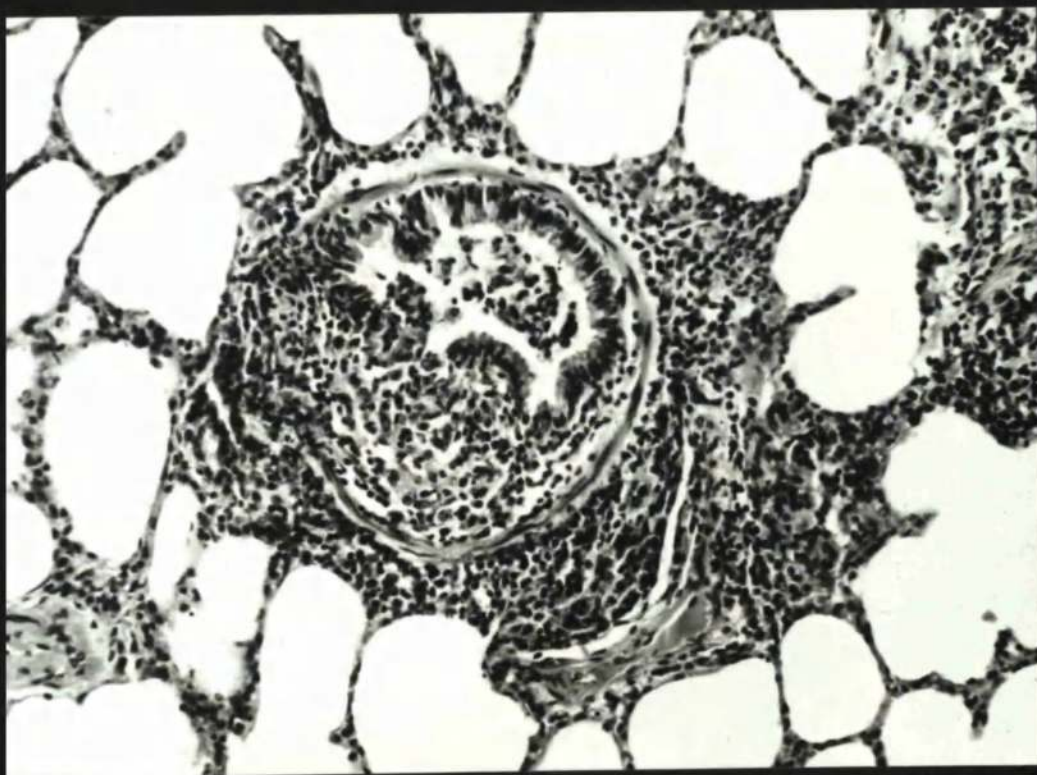
Fig. 77 Extrinsic allergic alveolitis: bronchiolitis obliterans with peribronchiolar infiltration of plasma cells and lymphocytes.

(H & E, x 300)

Fig. 78 Extrinsic allergic alveolitis: overinflation of acini and infiltration of alveolar walls by plasma cells, lymphocytes and multinucleated giant cells.

(H & E, x 300)

77



78

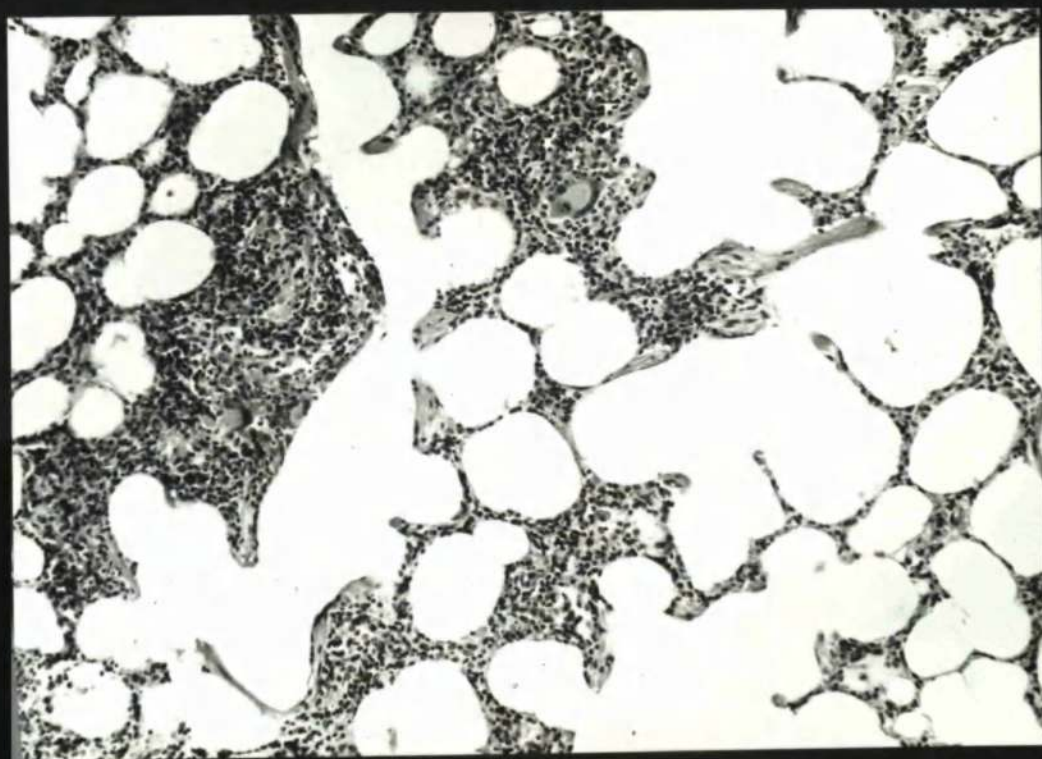


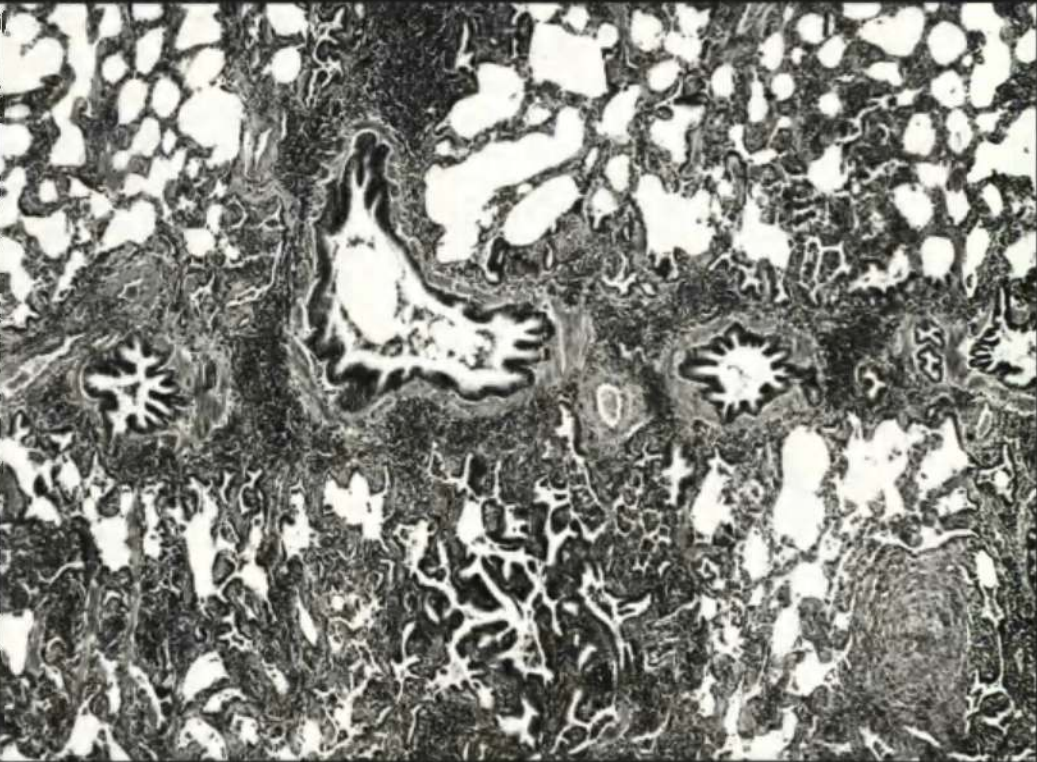
Fig. 79 Extrinsic allergic alveolitis: heavy infiltration of alveolar walls and peribronchiolar connective tissue by plasma cells and lymphocytes. Foci of alveolar epithelial hyperplasia and (lower centre) metaplasia. Epithelioid granulomata present also (lower right).

(H & E, x 110)

Fig. 80 Extrinsic allergic alveolitis: replacement of normal alveolar epithelium by tall, columnar ciliated cells.

(H & E, x 300)

79



80

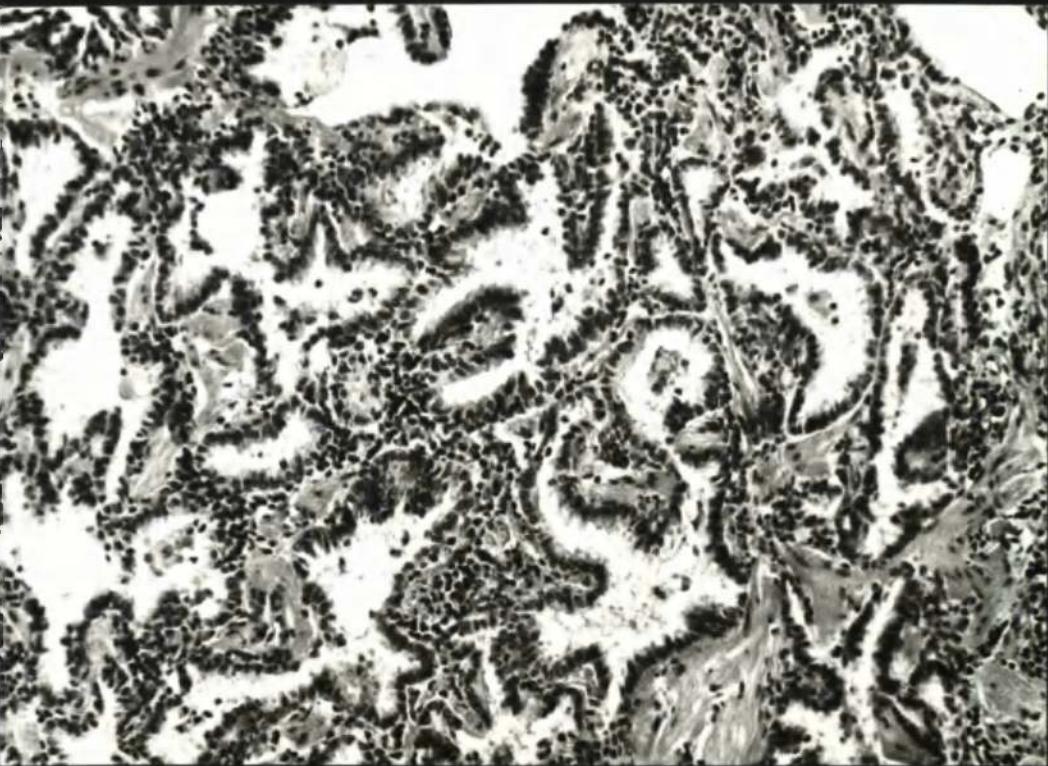
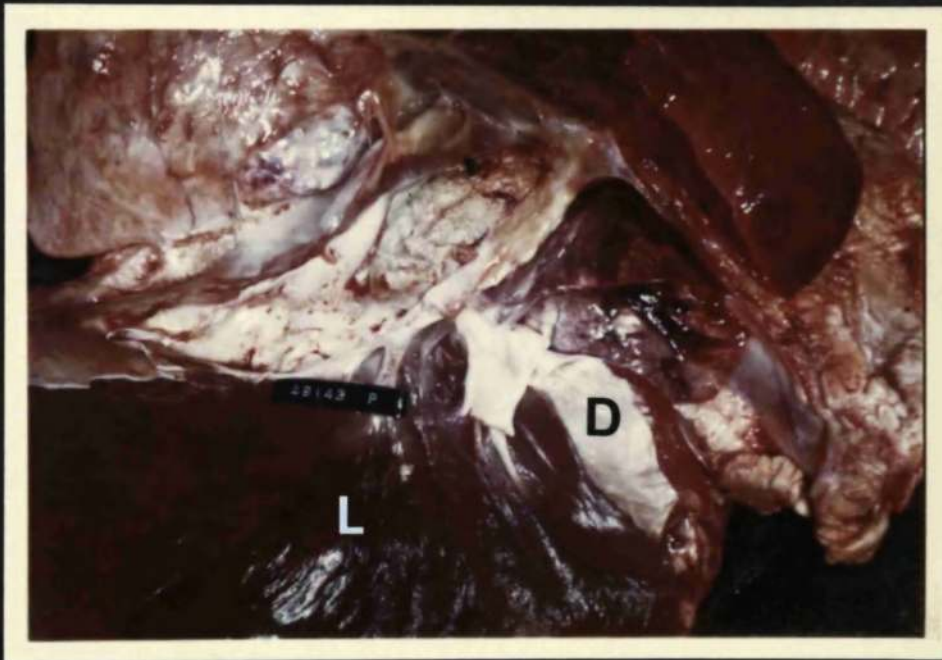


Fig. 81 septic thrombus in the posterior vena cava, mainly in the thoracic portion (liver L and diaphragm, D).

Fig. 82 close up of Fig. 81 . Septic thrombus at entrance to right heart. Note red lobules (top left and lower middle) filled with aspirated blood.

81



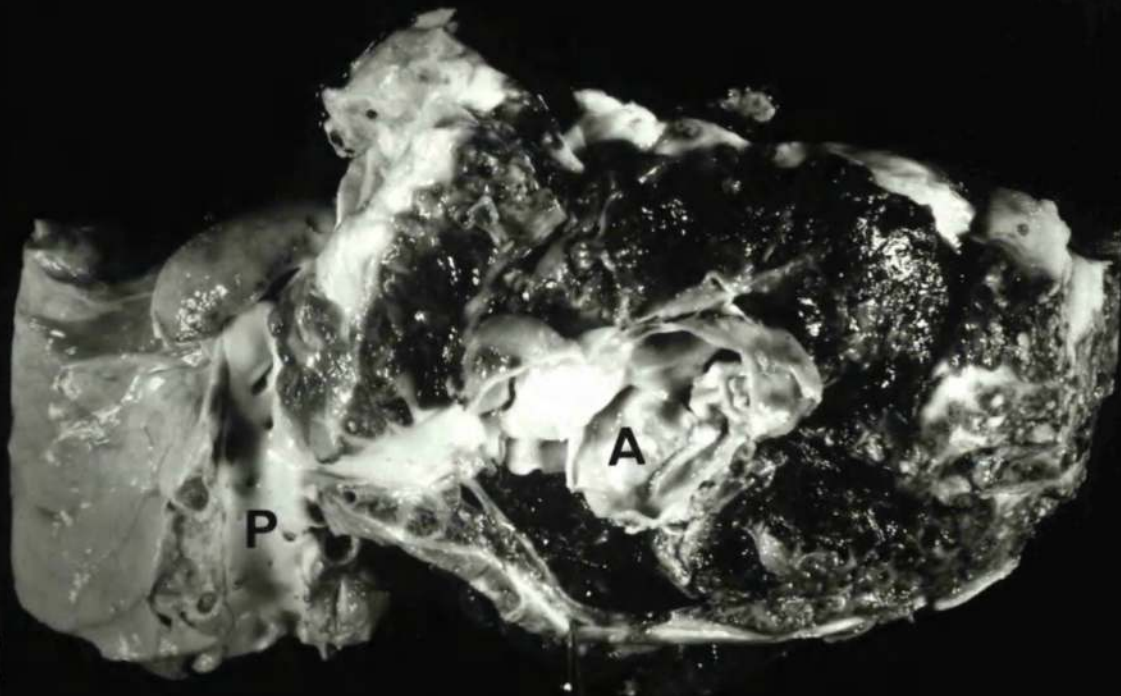
82



Fig. 83 Pulmonary thrombo-embolism: large aneurysm (A) of lobar branch of pulmonary artery (P). The aneurysm has ruptured releasing blood into an area of chronic suppurative pneumonia (right), involving most of the lobe.

Fig. 84 Thrombosis of posterior vena cava: severe chronic venous congestion of the liver when the posterior vena cava is totally occluded by a thrombus (T).

83



84

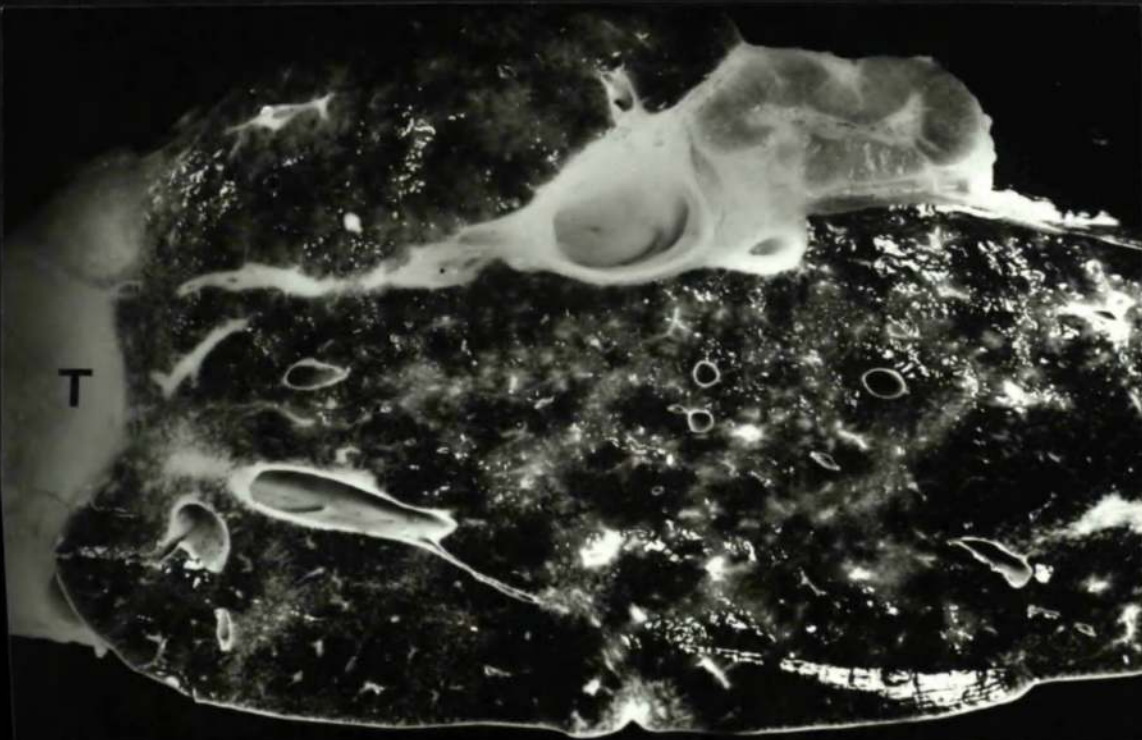
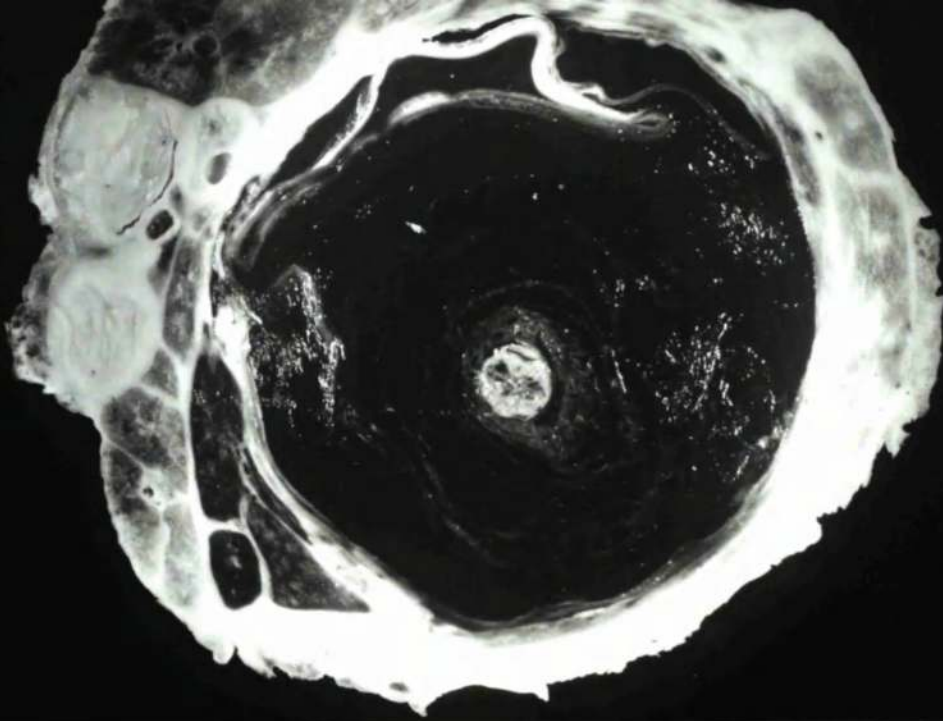


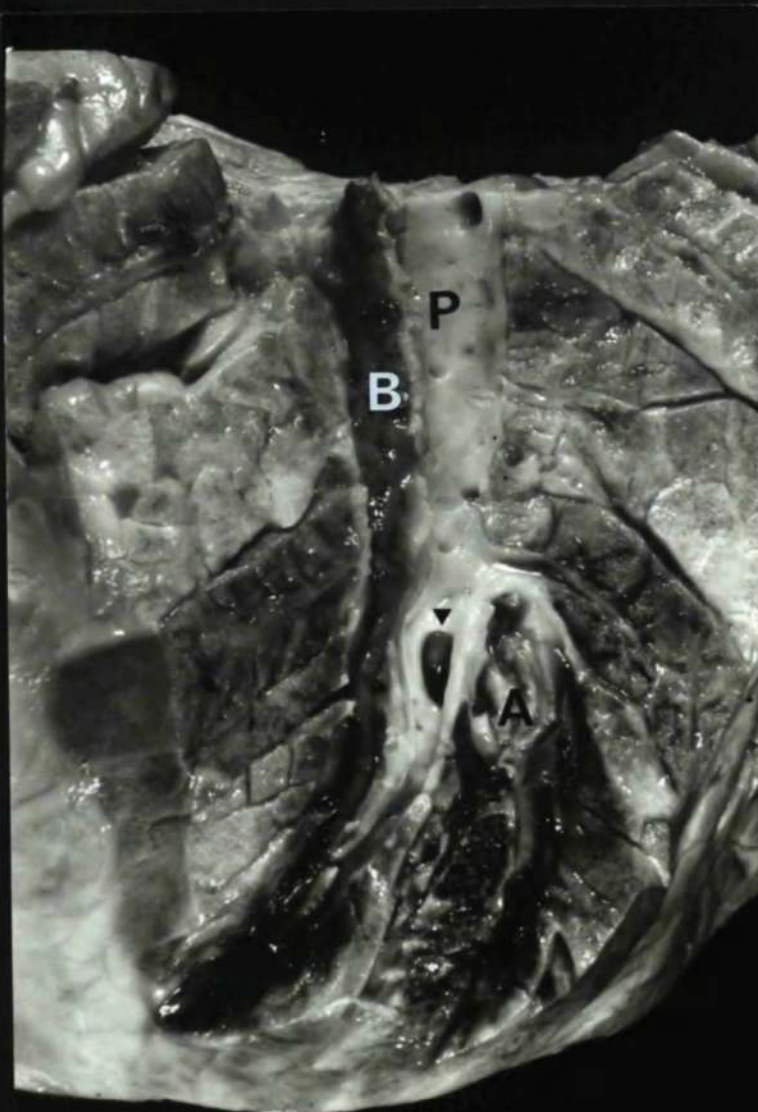
Fig. 85 Pulmonary thrombo-embolism: lamellated mass of clotted blood in interlobular connective tissue of lung. Wall of pulmonary arterial aneurysm can be seen (top). Two abscesses (left) and lobules filled with aspirated blood are also present.

(formalin fixed specimen)

Fig. 86 Pulmonary thrombo-embolism: blood clot fills bronchus (B) next to branch of pulmonary artery (P). An aneurysm has formed (arrow) in the vessel, adjacent to an abscess in the pulmonary parenchyme (A).



85



86

Fig. 87 ruptured aneurysm in the pulmonary artery (arrow) with lamellated mass of clotted blood in the interstitial tissues about the vessel. Red lobules (left) are filled with aspirated blood.

87



Fig. 88 Reinfection husk: overinflation of lobules, especially in cardiac lobe. Mild interstitial emphysema in diaphragmatic lobe with single bulla (top). Pulmonary lymphoid nodules are visible (arrow).

Fig. 89 Reinfection husk: slightly collapsed red lobules adjacent to several pulmonary lymphoid nodules (arrow).

88



89

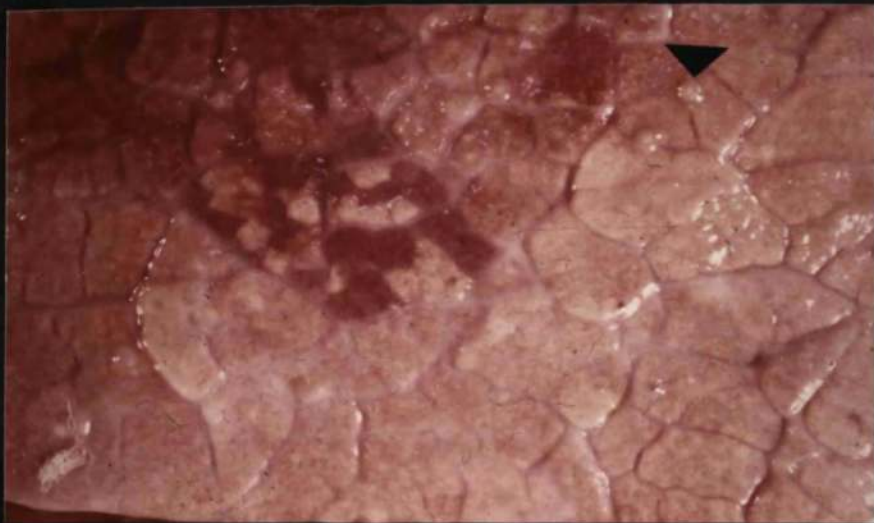


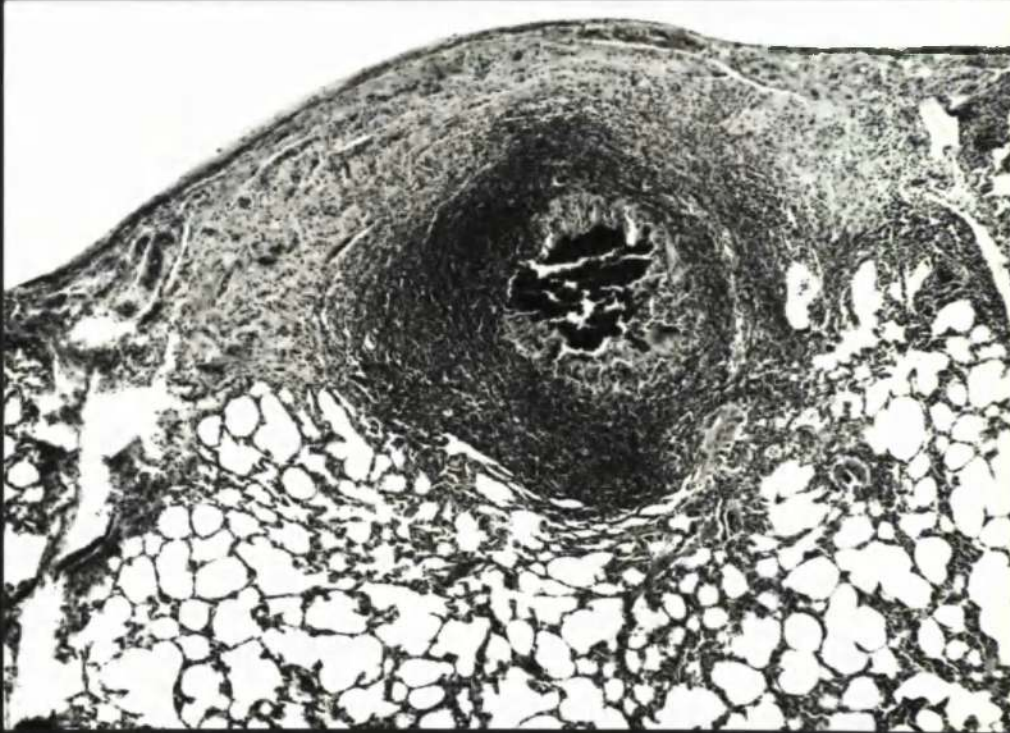
Fig. 90 Reinfection husk: pulmonary lymphoid nodules at periphery of lobule. The central core of eosinophilic parasitic debris is surrounded by macrophages, giant cells and epithelial cells. External to this is a thicker zone of lymphocytes, plasma cells and eosinophils.

(H & E, x 110)

Fig. 91 Reinfection husk: higher power view of Fig.

(H & E, x 300)

90



91

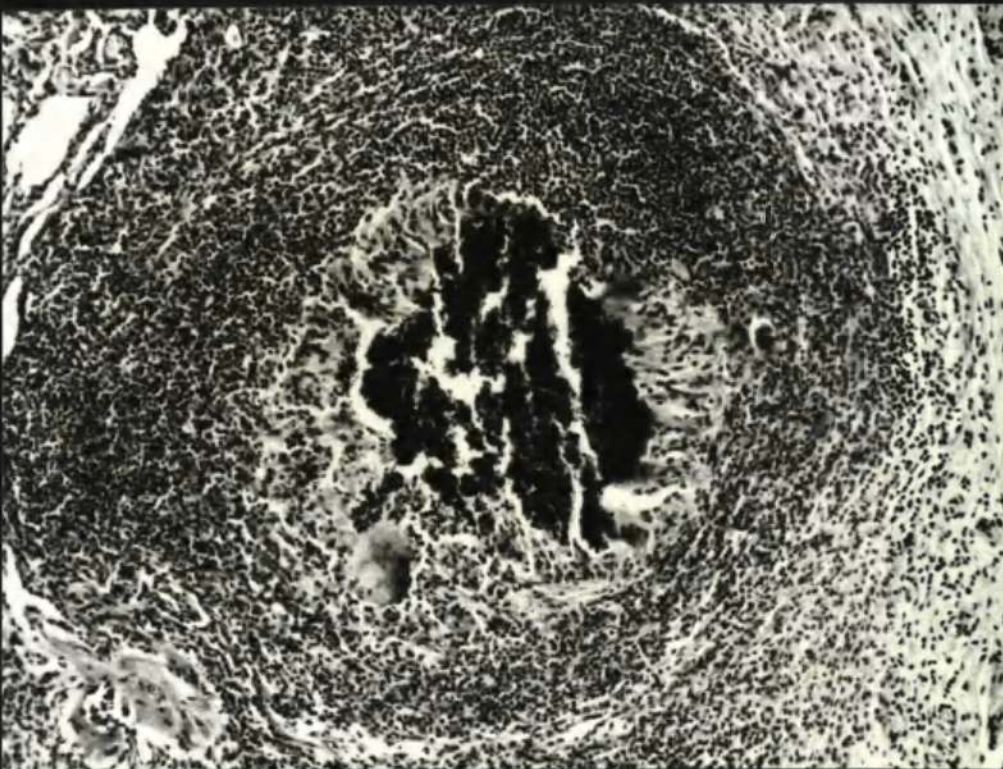


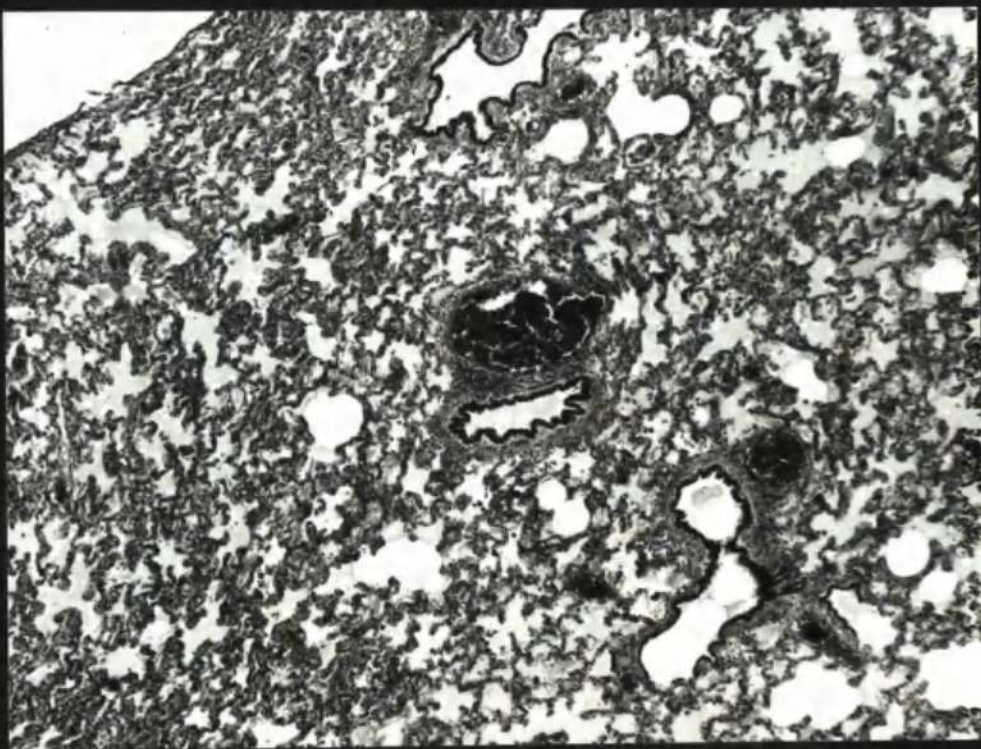
Fig. 92 Acute pulmonary oedema and interstitial emphysema:
severe pulmonary oedema with fine hyaline membranes
and congestion of septal capillaries.

(H+E, x 50)

Fig. 93 Acute pulmonary oedema and interstitial emphysema:
intra-alveolar haemorrhage, pulmonary oedema and
hyaline membranes and alveolar collapse.

(H+E, x 110)

92



93



Fig. 94 Acute pulmonary oedema and interstitial emphysema:
severe pulmonary oedema and intra-alveolar
haemorrhage.

(H+E, x 110).

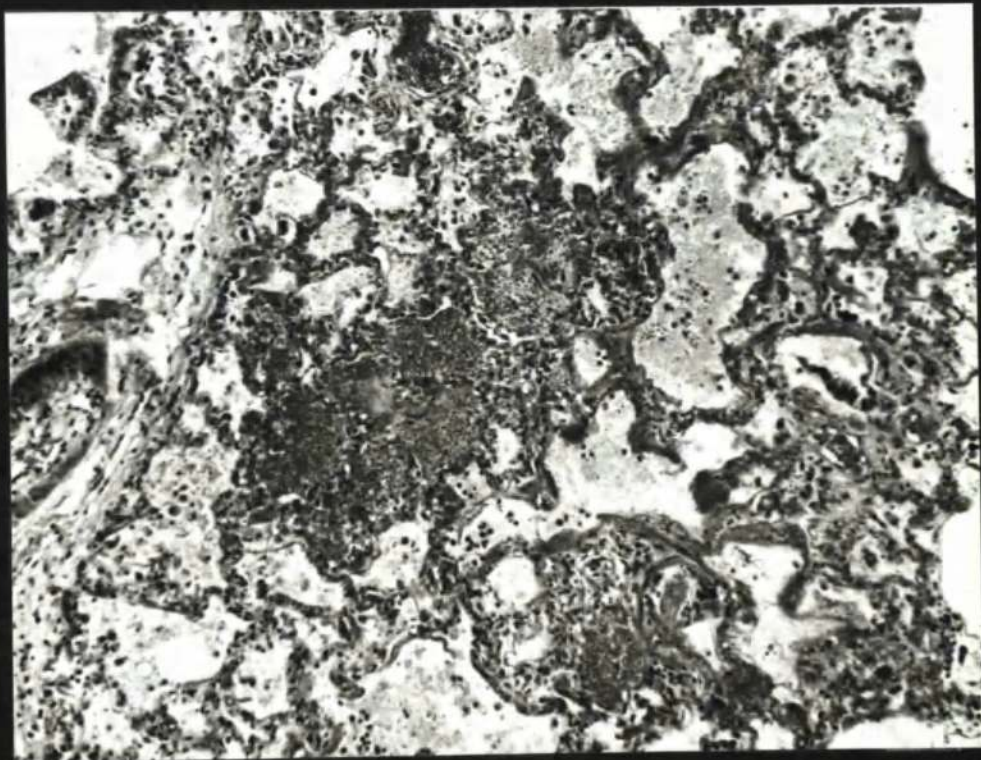


Fig. 95 Chronic suppurative pneumonia with multiple lung abscesses.

95

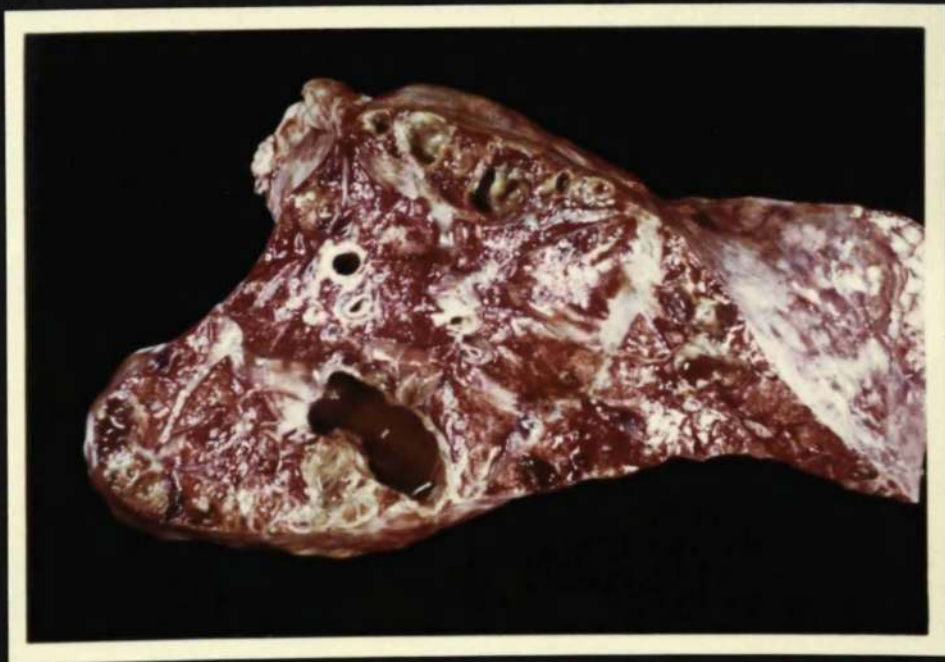


Fig. 96 Pre-patent parasitic bronchitis: severe interstitial and subpleural emphysema, note bulla in mid-ventral diaphragmatic lobe.

Fig. 97 Patent parasitic bronchitis: consolidated lobules, particularly along ventral edge of diaphragmatic lobe, and overinflation of remaining segments.

96



97



47482/B

Fig. 98 Post-patent parasitic bronchitis: extensive alveolar epithelial hyperplasia mainly confined to segments of dorsal diaphragmatic lobes. Remaining lobes are over-inflated.

Fig. 99 Post-patent parasitic bronchitis: diffuse alveolar epithelial hyperplasia involving all lung lobes. Pale area in caudal diaphragmatic lobe is an artefact.

98



99

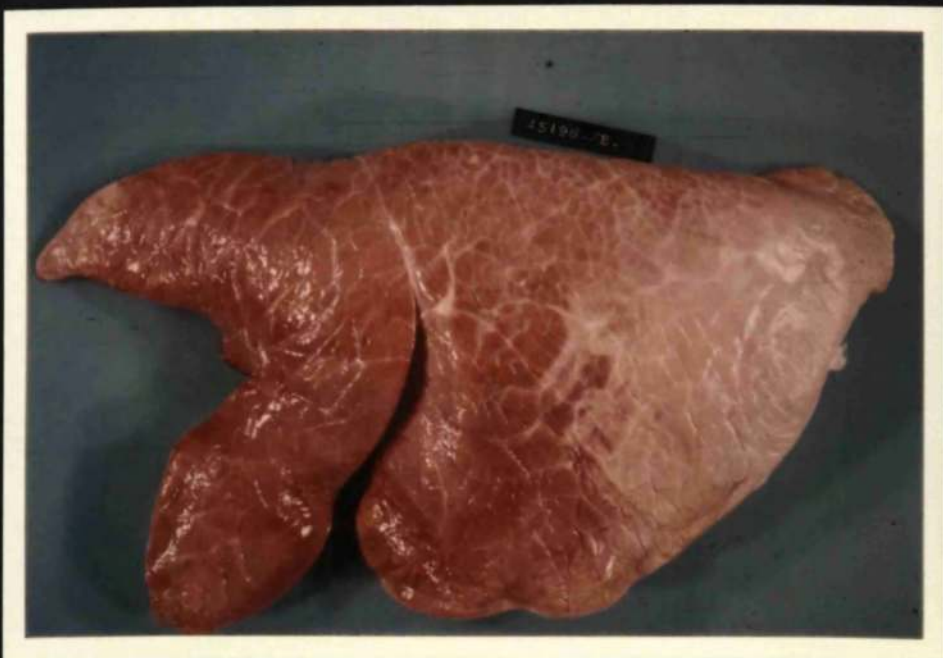
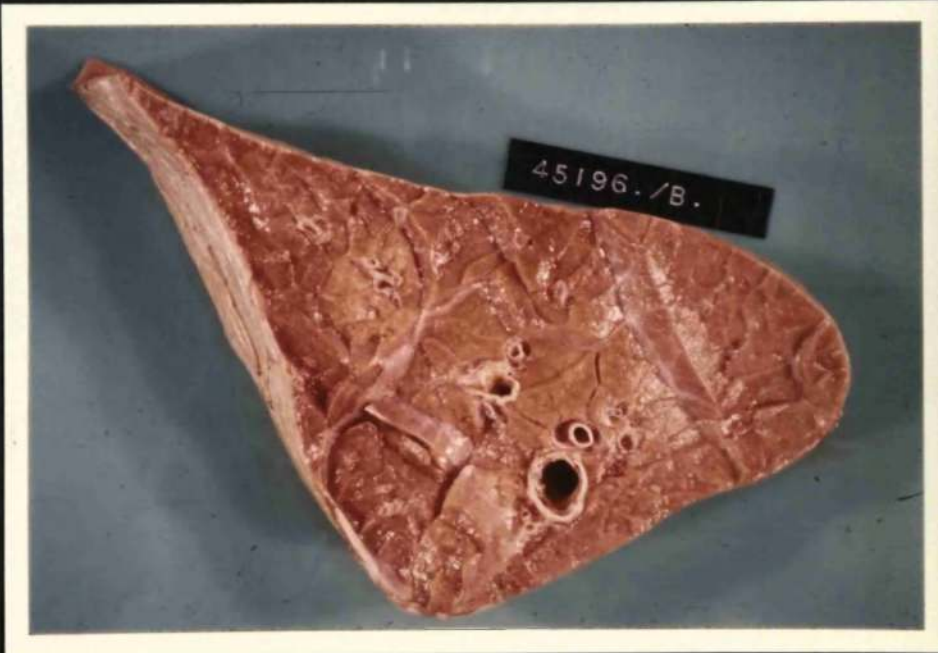


Fig. 100 Post-patent parasitic bronchitis: cross section of diaphragmatic lobe of lung illustrated in Fig. 99 .
Diffuse, alveolar epithelial hyperplasia with some perivascular and peribronchial gas tracking.

Fig. 101 Post-patent parasitic bronchitis: cross section of diaphragmatic lobe of lung illustrated in Figs. 99, 100.
Diffuse alveolar epithelial hyperplasia and red, consolidated lobules, residual lesion of the patent phase.

100



101



Case 6

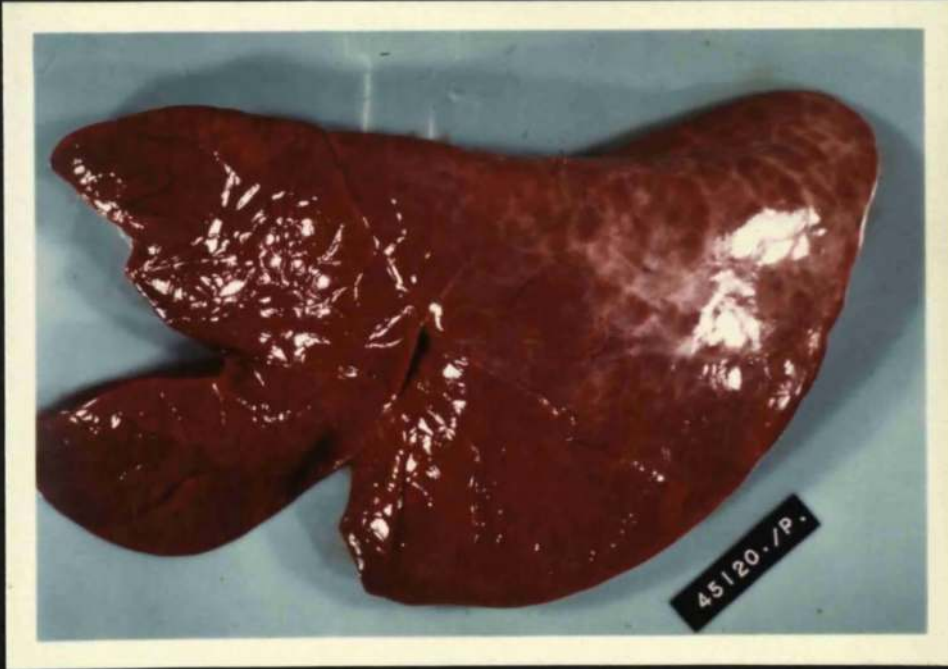
Fig. 102 There is interstitial emphysema in the dorsal diaphragmatic lobes but the rest of the lungs are dark red in colour, as a result of diffuse alveolar epithelial hyperplasia and congestion.

Case 1

Fig. 103 Pulmonary oedema with many macrophages and neutrophils in the alveolar spaces and bronchiole. There is also congestion of the septal capillaries and proliferation of alveolar epithelial cells.

(H+E, x 110)

102



103



Case 3

Fig. 104 congestion of alveolar septal capillaries and
alveolar epithelial hyperplasia.

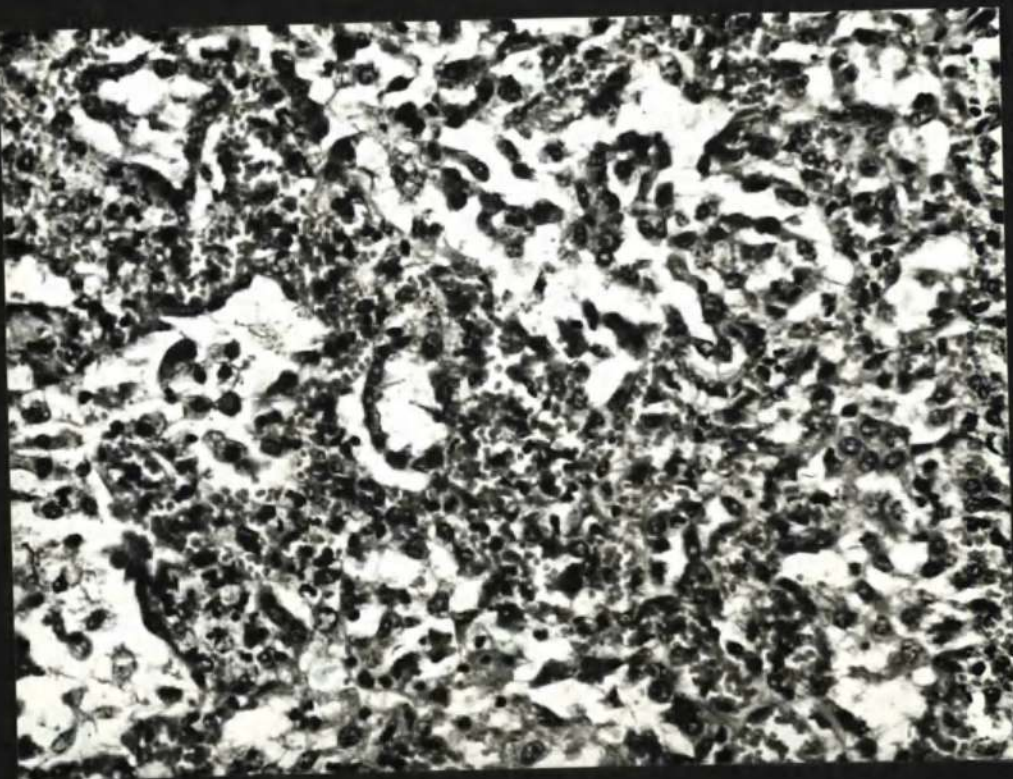
(H+E, x 300)

Case 2

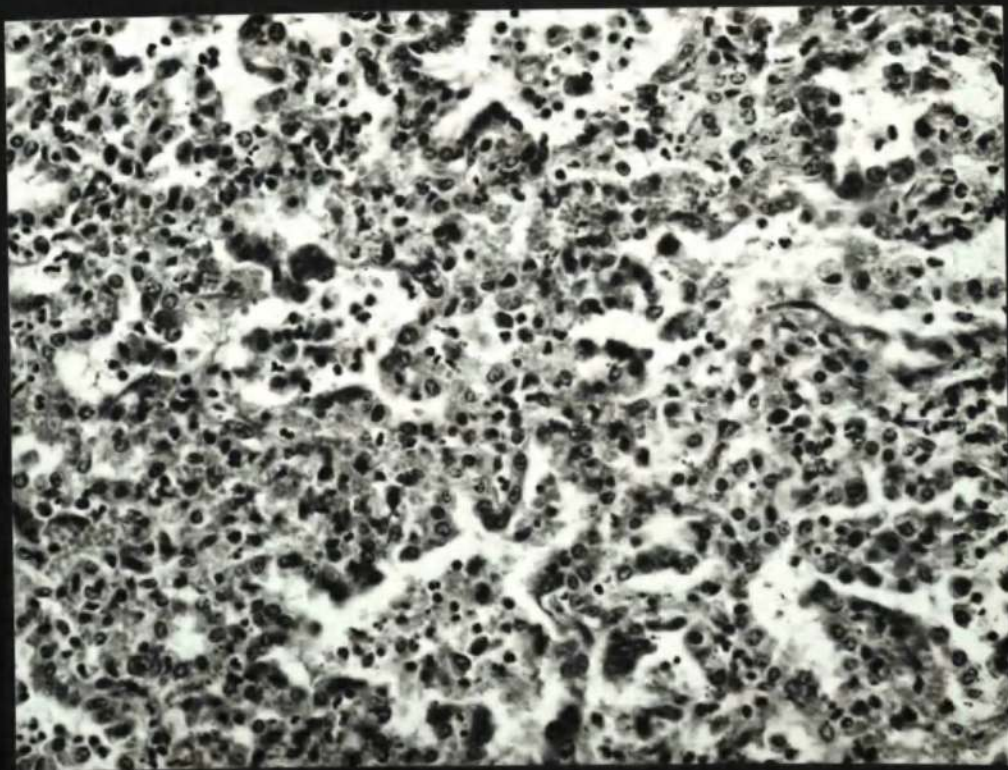
Fig. 105 congestion of alveolar septal capillaries, alveolar
epithelial hyperplasia and exudate of neutrophils
and alveolar macrophages in alveolar spaces.

(H+E, x 300)

104



105



Case 10

Fig. 106 pulmonary oedema, hyaline membranes and
proliferation of alveolar epithelial cells.

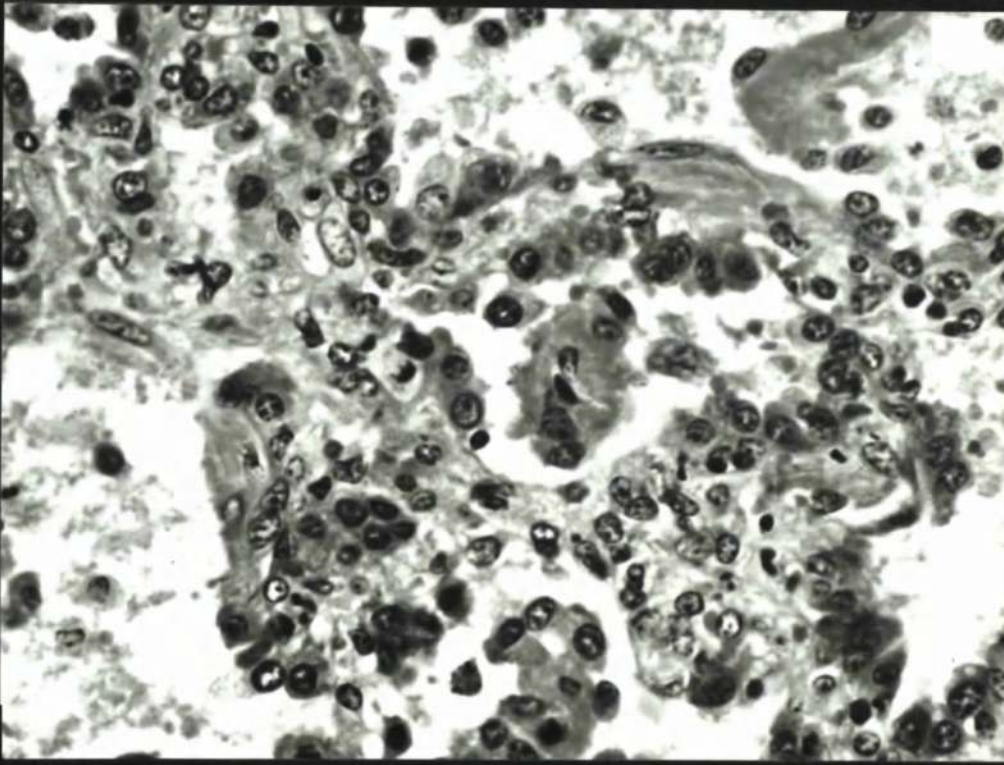
(H+E, x 500)

Case 12

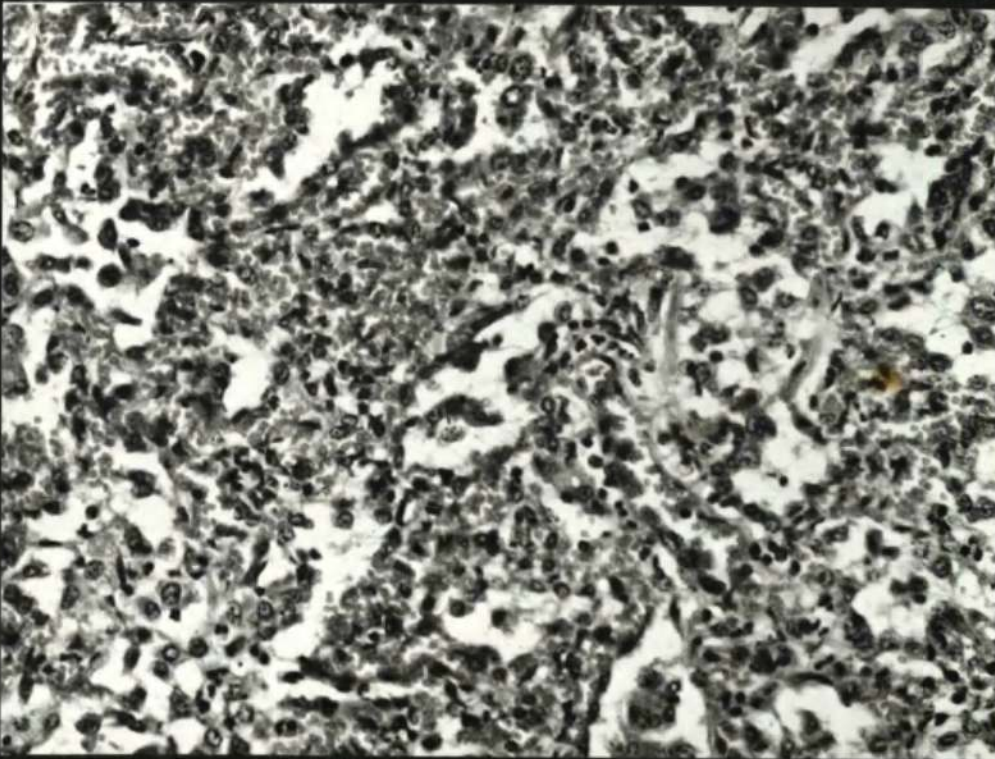
Fig. 107 congestion of alveolar septal capillaries and
proliferation of alveolar epithelial cells.

(H+E, x 300)

106



107



FIGURES FOR ELECTRON MICROSCOPY

AND HISTOCHEMISTRY

Fig. 109 Bovine lung: macrophages in alveolar spaces (M), type 2 pneumonocytes (2) with possible type 1 pneumonocytes (1) and capillary endothelial cell (C). Interstitial cells (arrow) are also marked.
(Toluidine blue thick section: x 500).

Fig. 110 Fog fever: proliferating type 2 pneumonocytes, some some of which contain small dark granules (arrow). There is oedema of alveolar septa and an increased number of interstitial cells.
(Toluidine blue thick section : x 900).

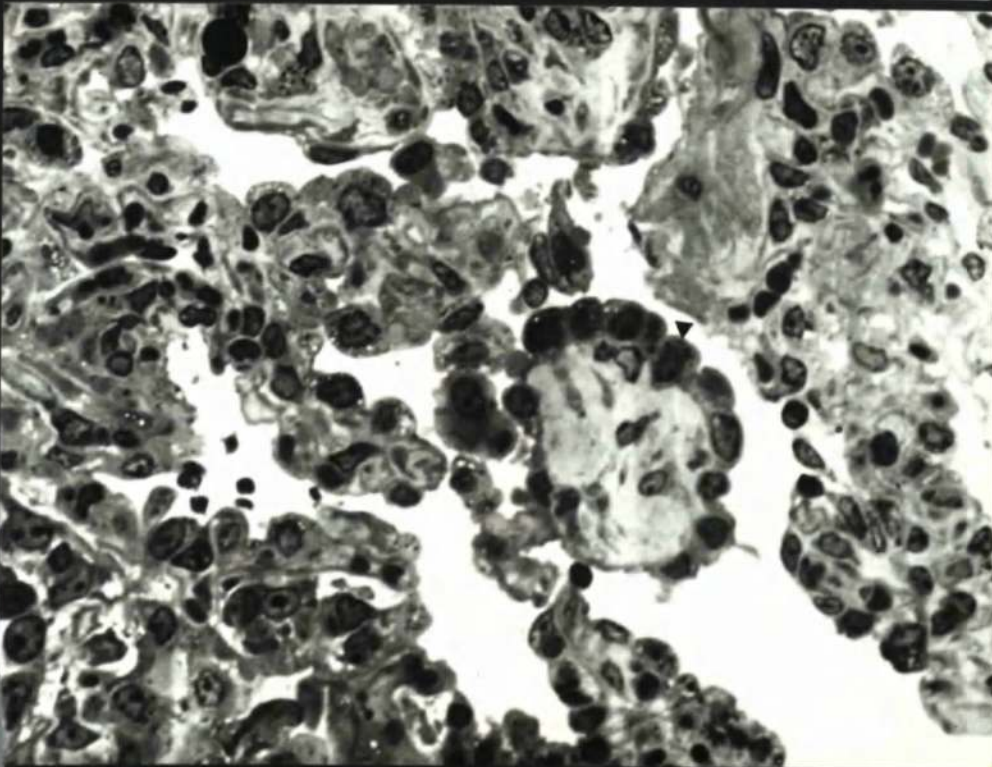
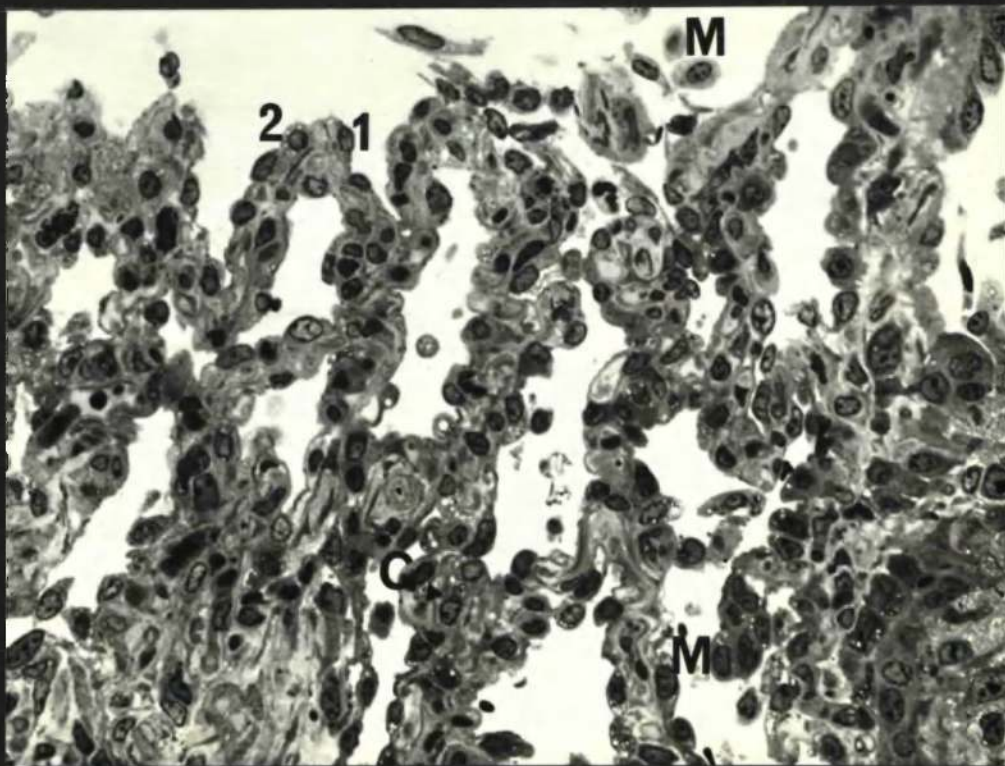


Fig. 111 Bovine lung: terminal bronchiolar lumen (BL) opening into alveolar duct (AD). Bronchiolar cells (B) abut onto type 1 pneumonocyte cytoplasm (1). Smooth muscle of alveolar duct (S) and cilia (top right) are also visible.

(OsO₄, x 10,000)

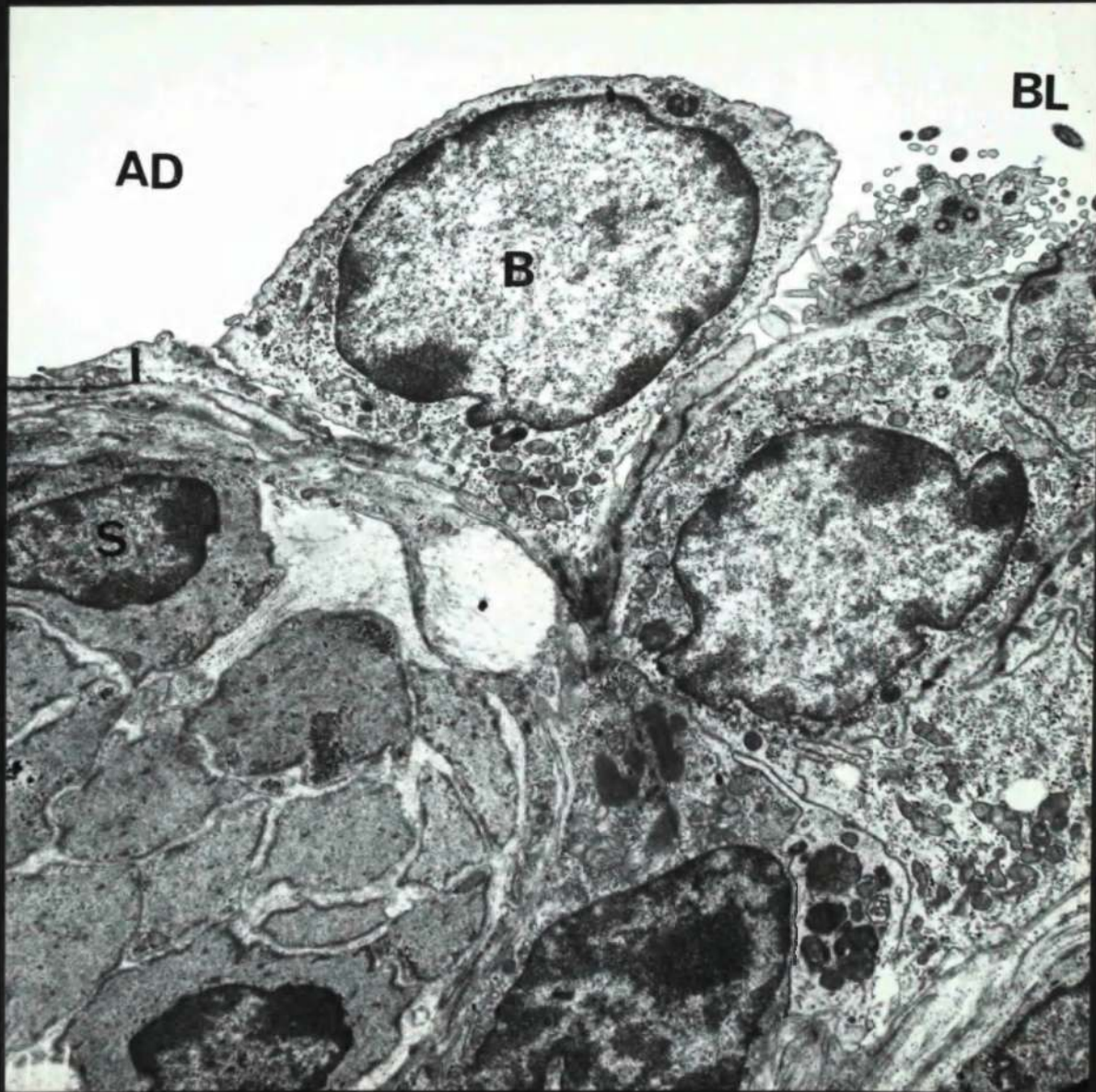


Fig. 112 Bovine lung: alveolar spaces (AS) lined by type 1 (1) or type 2 (2) pneumonocytes. Capillary, lined by endothelial cells (EC) bulges into alveolus; minimal blood: air barrier formed by cytoplasm and basement membranes of the type 1 pneumonocyte and capillary endothelial cell (arrow). Smooth muscle cell (S) visible in interstitium. Monocyte (M), in capillary lumen, contains lysosomes. Type 2 pneumonocyte (lower right) is at the angle of the alveolus: in this position it has been referred to as a 'niche cell'.

(OsO₄, x 6000)



Fig. 113 Bovine lung: the alveolar wall separates two alveolar spaces (AS). A capillary (CL) traverses the wall and bulges into the alveolar lumen. Endothelial cells (EC) and an interstitial cell (IC) containing lysosomes are also present. Long cytoplasmic extensions of type 1 pneumocytes cover both alveolar surfaces, but the nuclei are not visible.

(OsO₄, x 10,000)

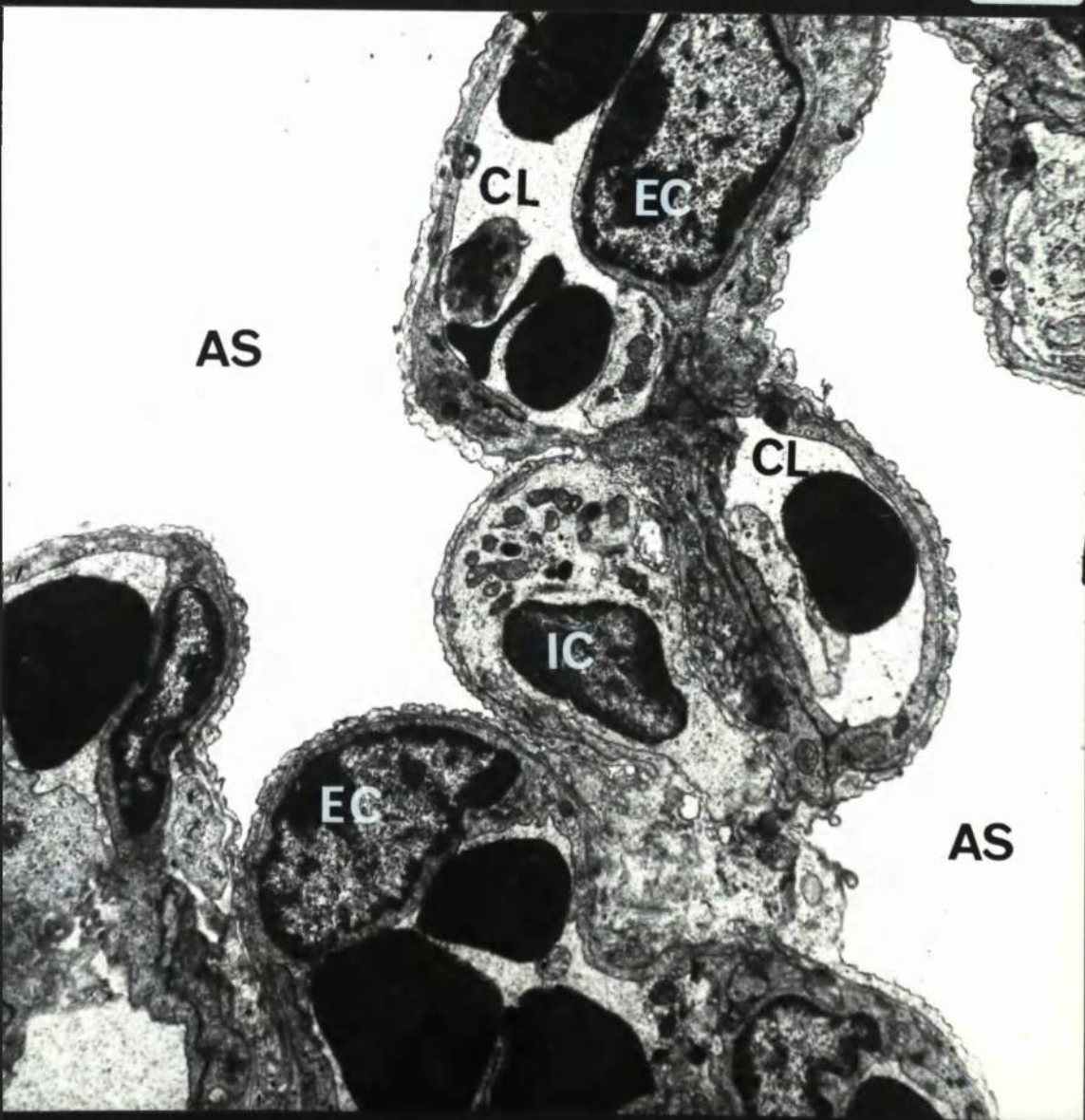


Fig. 114 Bovine lung: capillary (CL), containing red blood corpuscle (R), traverses alveolar wall between two alveolar spaces (AS). The attenuated cytoplasm of a type 1 pneumonocyte covers the alveolar wall on the left; the nucleus of a type 1 pneumonocyte (1) is visible (top right). The cytoplasm and nucleus of interstitial cells (IC) are visible between the epithelium and the capillary endothelium.

(OsO₄, x 10,000)

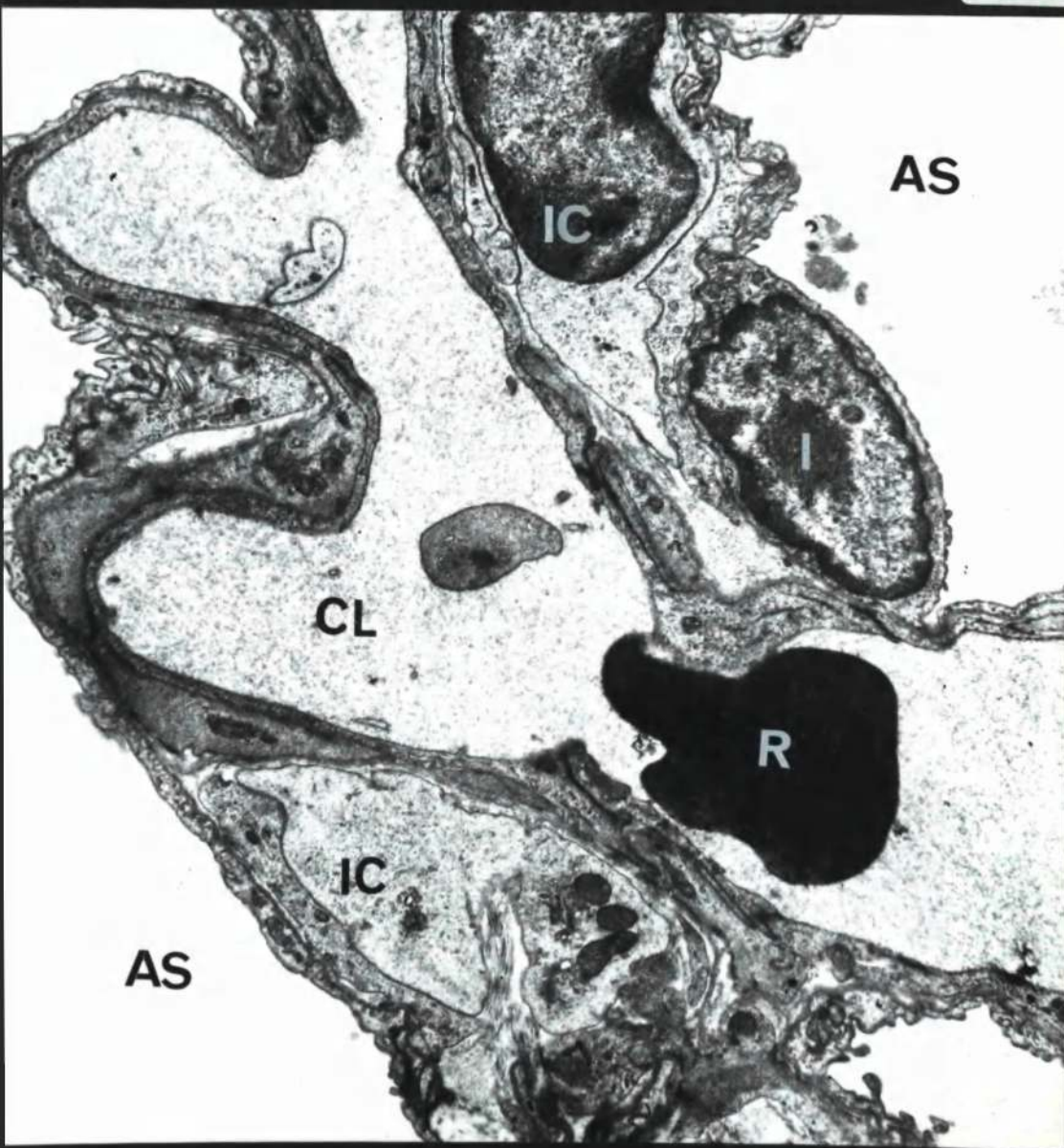


Fig. 115 Bovine lung: the junctional complex between two adjacent type 1 pneumonocytes is indicated (large arrow). The junction between two capillary endothelial cells (small arrows) is also marked. The alveolar space (AS) is separated from the capillary lumen (CL) by the cytoplasm of both a type 1 pneumonocyte and a capillary endothelial cell, and their fused basement membranes. The fused basement membranes separate (open small arrows) and in the tissue space so formed there is a portion of cell cytoplasm (CP); this could be from a pericyte or an interstitial cell.

(OsO₄, x 40,000)

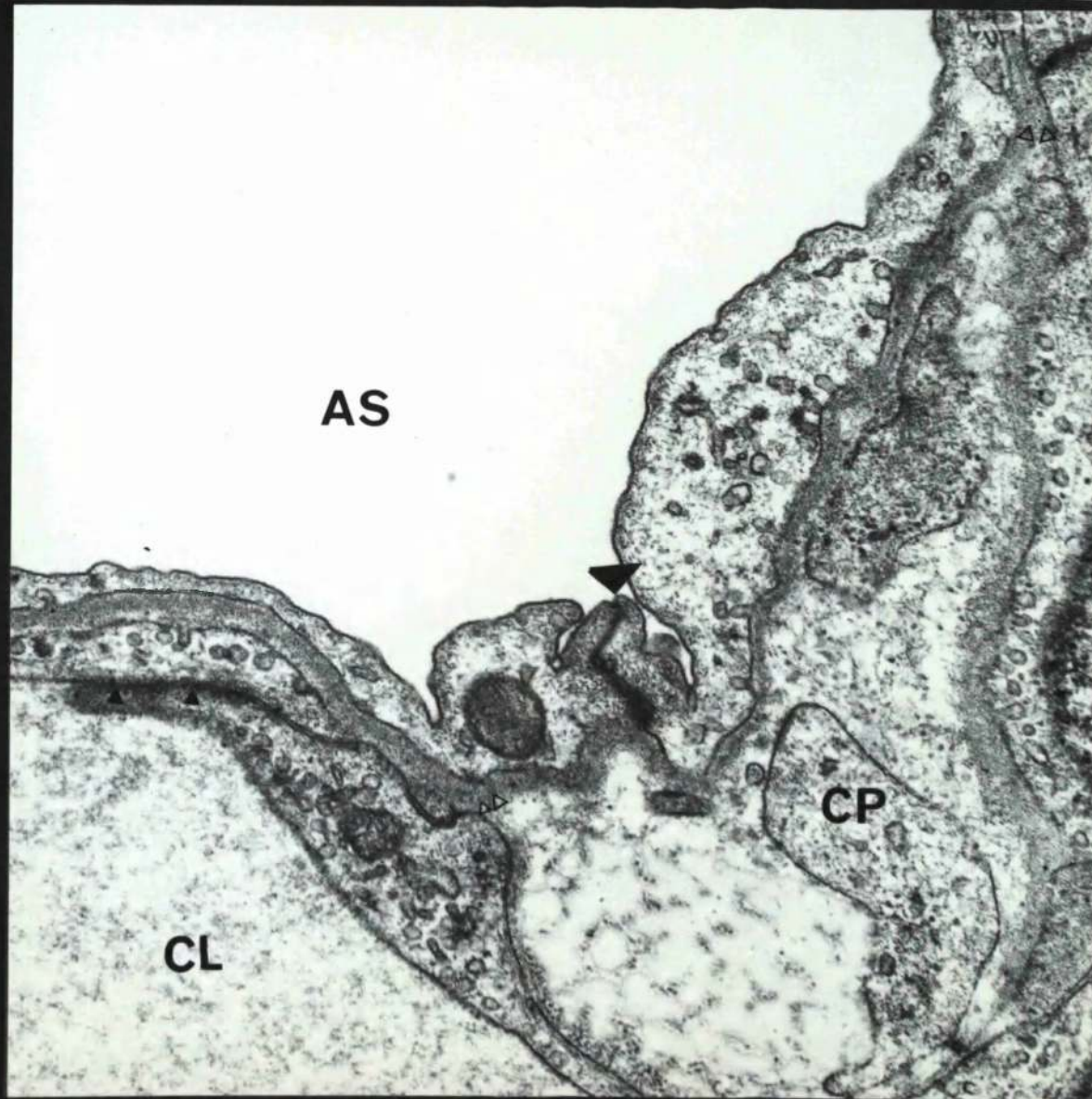


Fig. 116 Bovine lung: the blood : air barrier.

The alveolar space (AS), and capillary lumen (CL) are separated by attenuated type 1 cell cytoplasm (1), fused epithelial and endothelial basement membranes (B) and attenuated capillary endothelial cell cytoplasm (EC). Many pinocytotic vesicles are apparent, particularly in the endothelial cell cytoplasm.

(OsO₄, x 40,000)

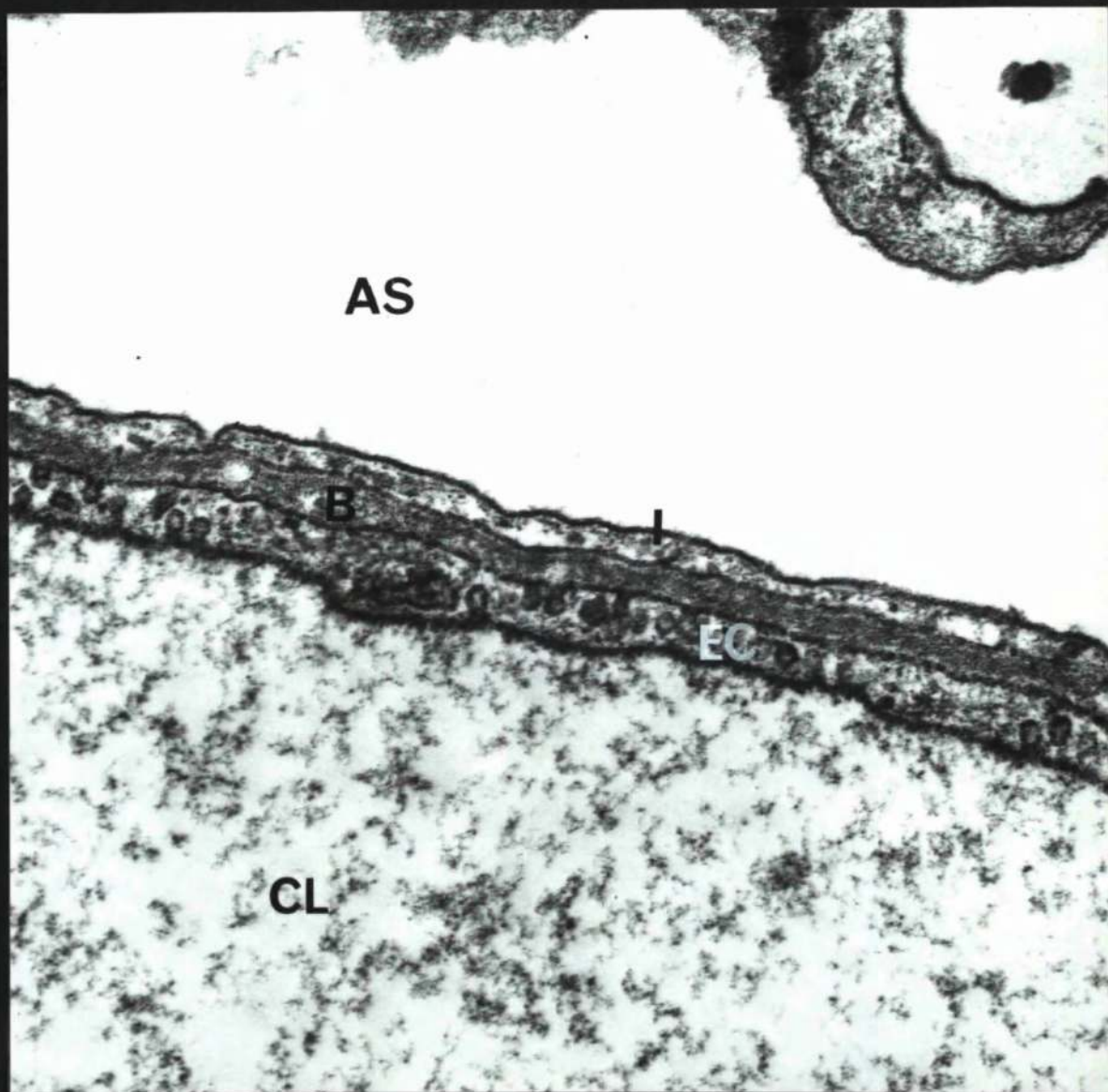


Fig. 117 Bovine lung: a type 2 pneumonocyte (2) projects into an alveolar space (AS). The free surface of the cell is thrown into numerous short microvilli and variably electron dense inclusions are present in the apical cytoplasm. An interstitial cell (IC) lies beneath the epithelium and sends processes between the epithelium and the endothelium of the capillary (CL) on the left of the photograph

(OsO₄, x 10,000)

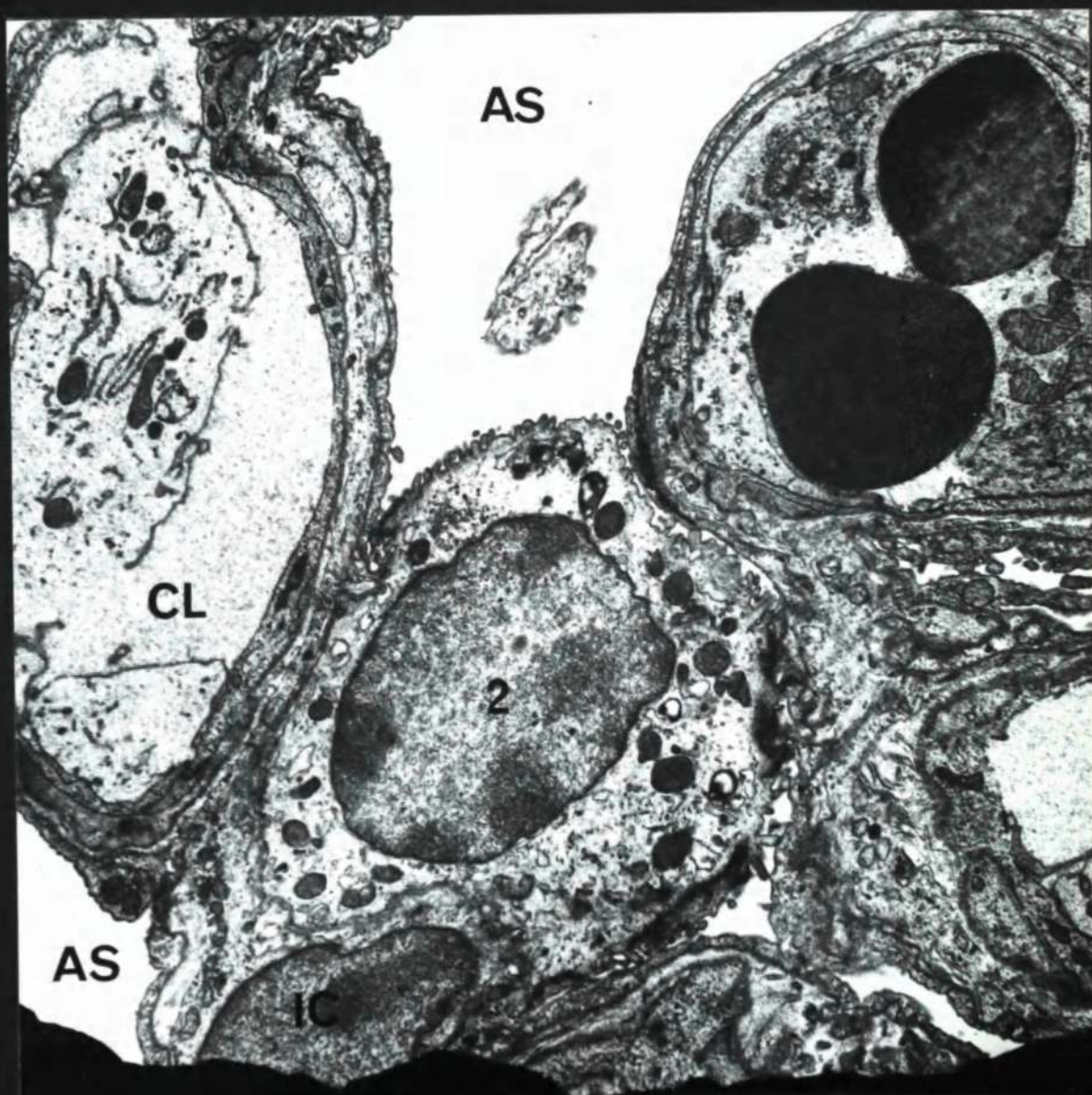


Fig. 118 a & b, junctional complex between a type 2 and a type 1 pneumonocyte. The zonula occludens (ZO), zonula adhaerens (ZA) and macula adhaerens (MA) or desmosome are indicated.

(Figure 118 a, x 40,000, 1% OsO_4
and Figure 118 b, x 80,000, 1% OsO_4)

118a

118b

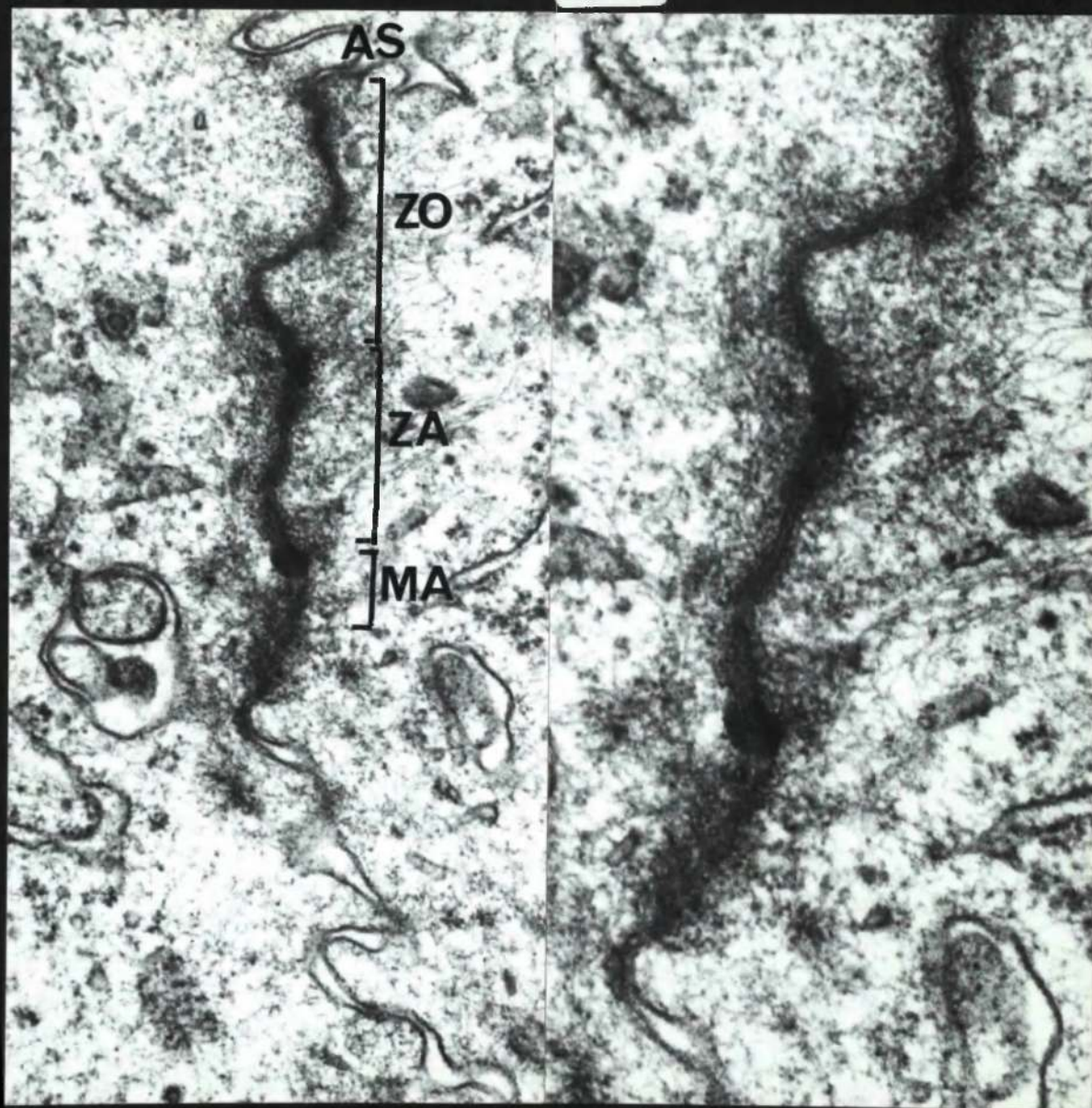


Fig. 119 Bovine lung: two type 2 pneumonocytes (2) project into the alveolar space (AS). Microvilli are present in the free surface of these cells, which rest on a basement membrane (single arrows). Variably electron dense, irregular inclusions (IB) are found in the cytoplasm. Extensions of type 1 pneumonocyte cytoplasm (double arrow) cover a part of the lateral surfaces of type 2 pneumonocytes. The cytoplasm of an interstitial cell (IC) is visible between the epithelial basement membrane and capillary endothelial basement membrane (small single arrows). A capillary (CL) fills the lower part of the figure.

(OsO₄, x 15,000)

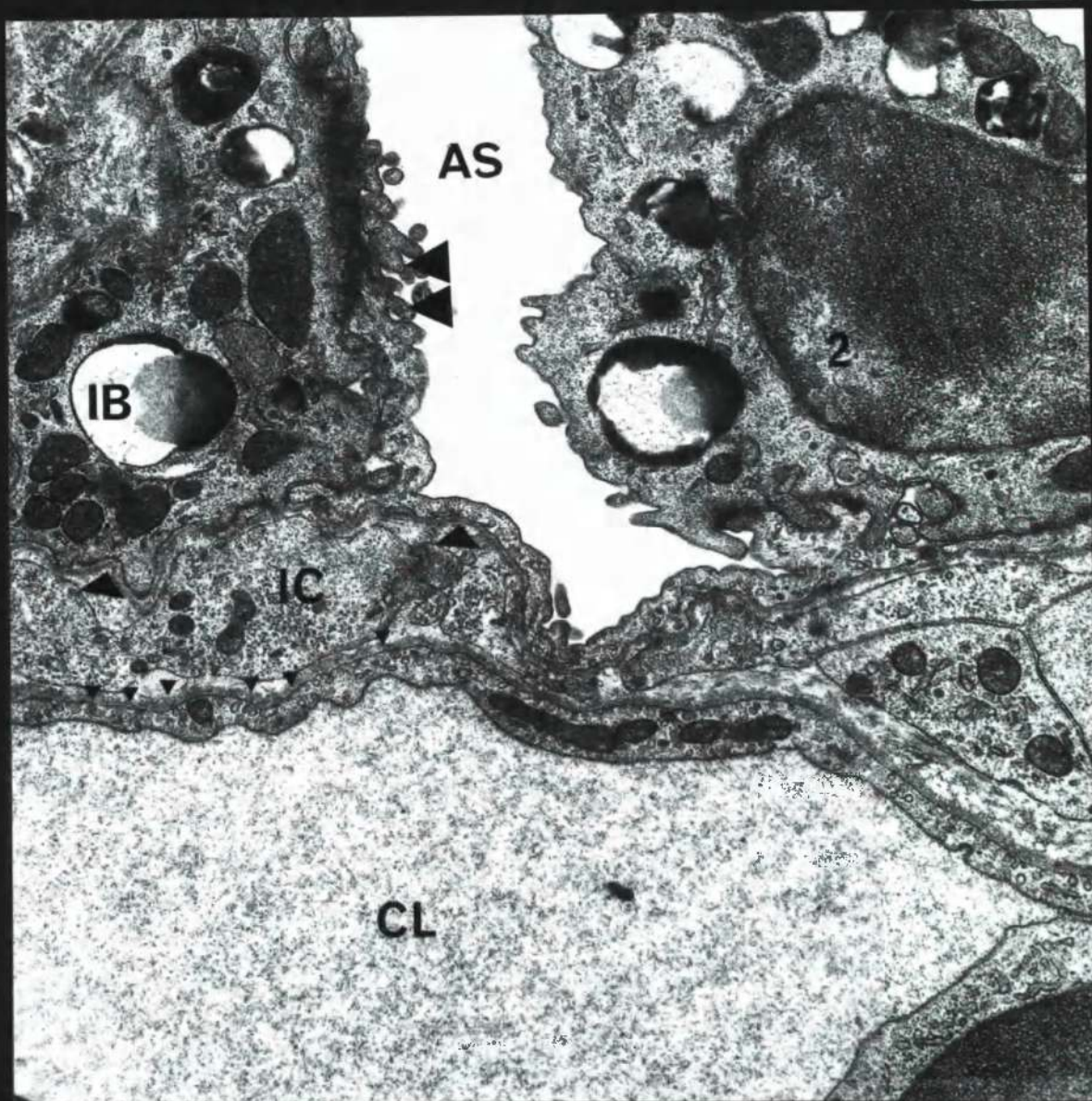


Fig. 120 Bovine lung: a type 2 pneumonocyte (2) projects into an alveolar space (AS). Very many variably electron dense inclusions are found in the cytoplasm of the cell; some of these are empty and lamellation of the contents is not marked in the others. In the alveolar septum, there is an interstitial cell (IC2) containing a few mitochondria and numerous large vesicles, partially filled with material of low electron density. A capillary endothelial cell (EC) is also present.

(OsO₄, x 10,000)

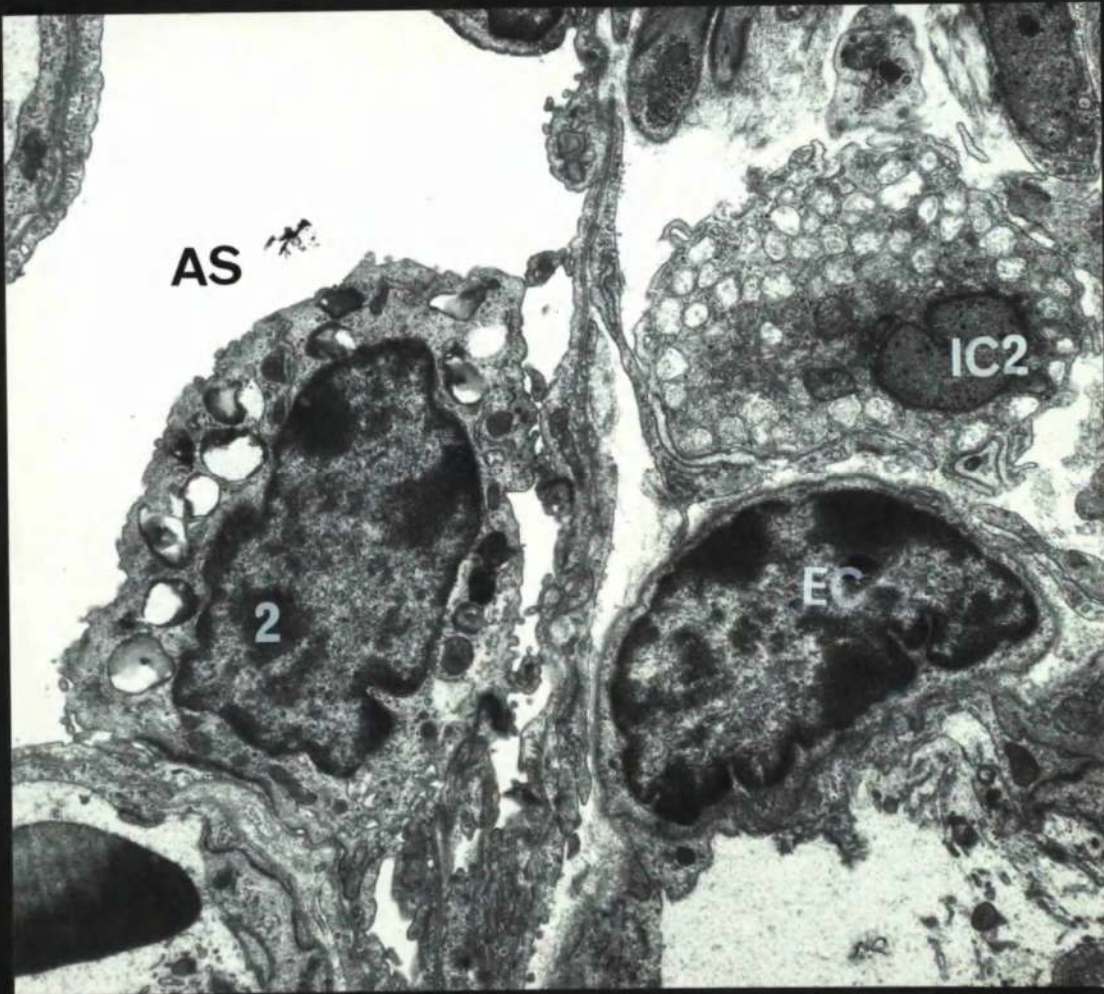


Fig. 121 membrane bound inclusion of type 2
 pneumonocyte

(1% OsO₄, x 60,000).



Fig. 122 Bovine lung: two type 2 pneumonocytes (2) project into the alveolar space (AS). This cuboidal cell has surface microvilli, rests on a basement membrane (small arrows) and forms junctional complexes (J) with adjacent cells (here another type 2 pneumonocyte - left). Many variably electron dense, lamellated inclusions (IB) are apparent in the apical cytoplasm. Multivesicular bodies (large arrow) are found near the Golgi apparatus (G). Many mitochondria, short profiles of rough surfaced endoplasmic reticulum (RSEr) and smooth surfaced endoplasmic reticulum (SSEr) are also visible. The inclusions of this cell are particularly ^{osmophilic} and dense.

(OsO₄, x 15,000)



Fig. 123 Bovine lung: a macrophage (M) lies free in the alveolar lumen. The cell surface is thrown into long projections and several phagosomes, containing myelin-like figures, are found in the cytoplasm. These figures may be contrasted with the inclusions of a type 2 pneumonocyte (lower left).

(OsO₄, x 15,000)

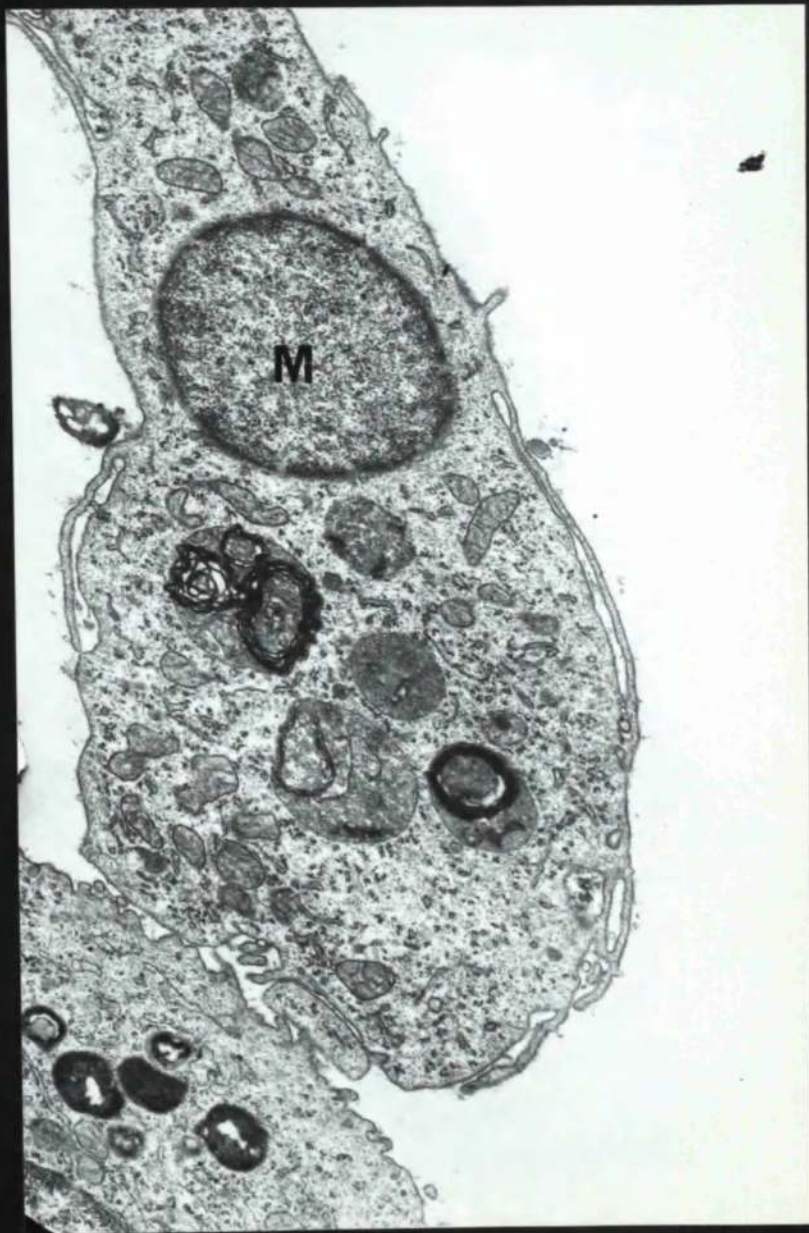


Fig. 124 Bovine lung: an alveolar macrophage (M) lies free in the alveolar lumen. A lysosome (arrow), fine filaments (F) and numerous mitochondria are present in the cytoplasm. The nucleus is slightly indented and the cell outline is irregular but not thrown into processes.

(OsO₄, x 15,000)

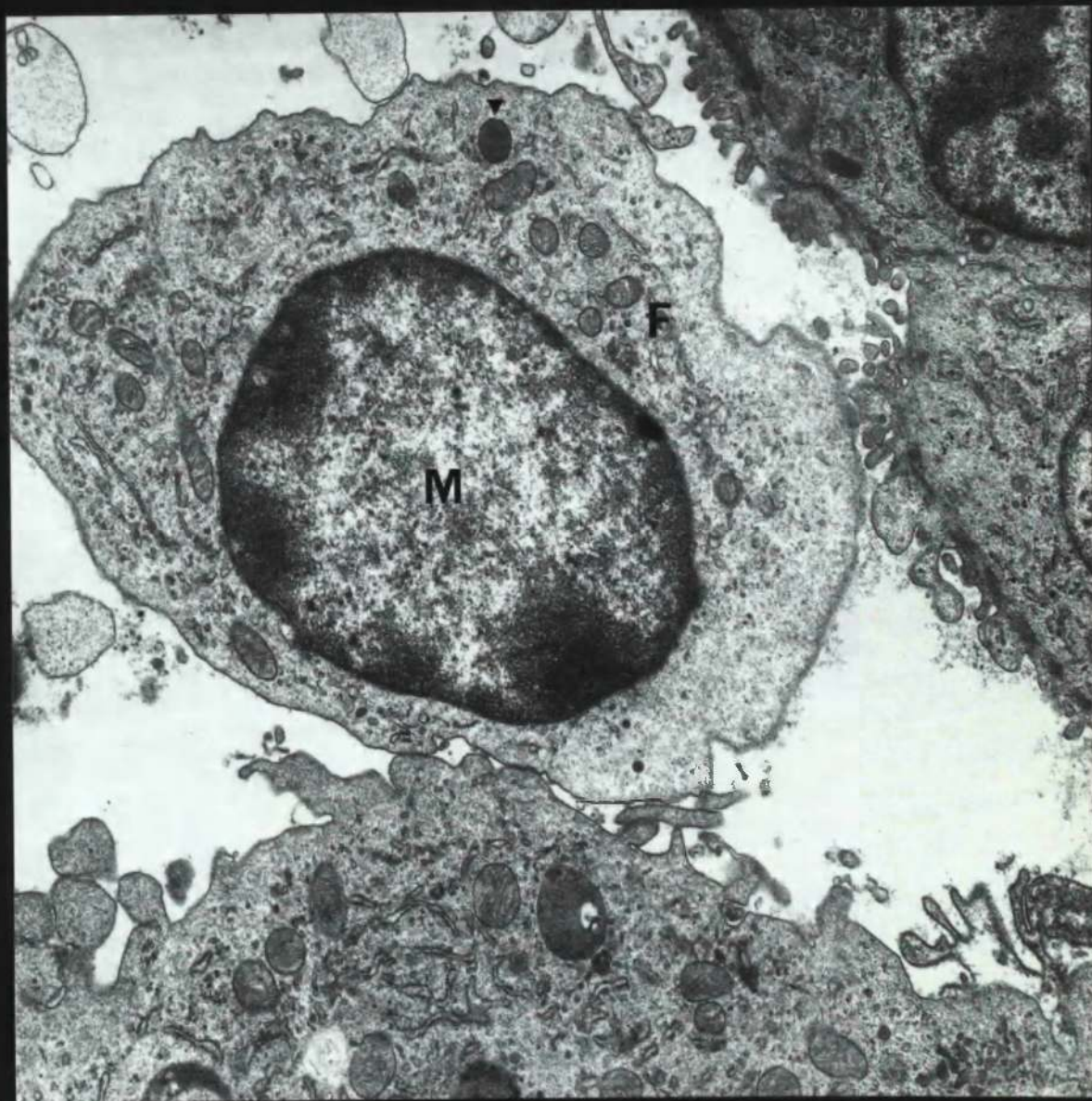


Fig. 125 Bovine lung: a capillary, lined by endothelial cells (EC), covered by the cytoplasm of a type 1 pneumonocyte, borders an alveolar space (AS). Many vesicles are apparent within the endothelial cell cytoplasm, complex interdigitations are formed at the junctions of adjacent endothelial cells (arrow). A smooth muscle cell (S) is found with elastic tissue in the interstitium. Part of a type 2 pneumonocyte (2) is visible in another alveolus (top centre).

(OsO₄, x 10,000)



Fig. 126 Bovine lung: the cytoplasm of a type 1 pneumonocyte (1) lines an alveolar space (AS) and covers a capillary and elastic tissue (E) in the alveolar wall. A pericyte (P) partially surrounds the capillary and is enveloped in basement membrane (small arrows) which splits at the points indicated (large arrows). A monocyte (M) and two red blood corpuscles are visible in the capillary lumen.

(OsO₄, x 10,000)

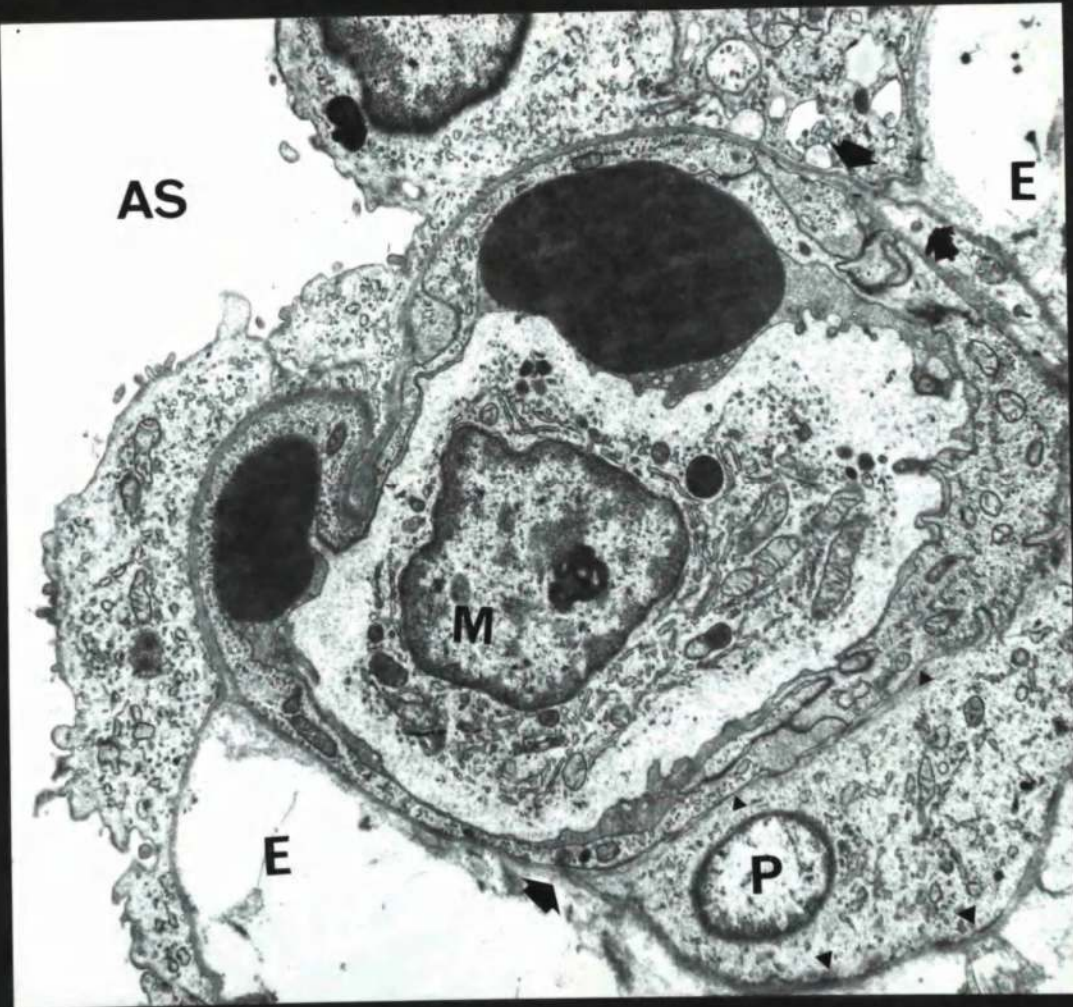


Fig. 127 Bovine lung: a pericyte (P), containing a few vesicles and mitochondria, is enveloped by basement membrane (small arrows) on all sides. The basement membrane splits (large arrow) to surround the cell. The capillary lumen is filled by a monocyte (M) containing lysosomes. Elastic tissue (E) borders the capillary.

(OsO₄, x 15,000)



Fig. 128 Bovine lung: an interstitial cell (IC) lies in the alveolar wall separating two alveolar spaces (AS). The interstitial cell gives off long processes penetrating between the basement membranes of the epithelial and endothelial cells (right). A portion of a type 2 pneumonocyte is visible above the interstitial cell. A monocyte (M) is present in the capillary lumen (CL).

(OsO₄, x 6000)

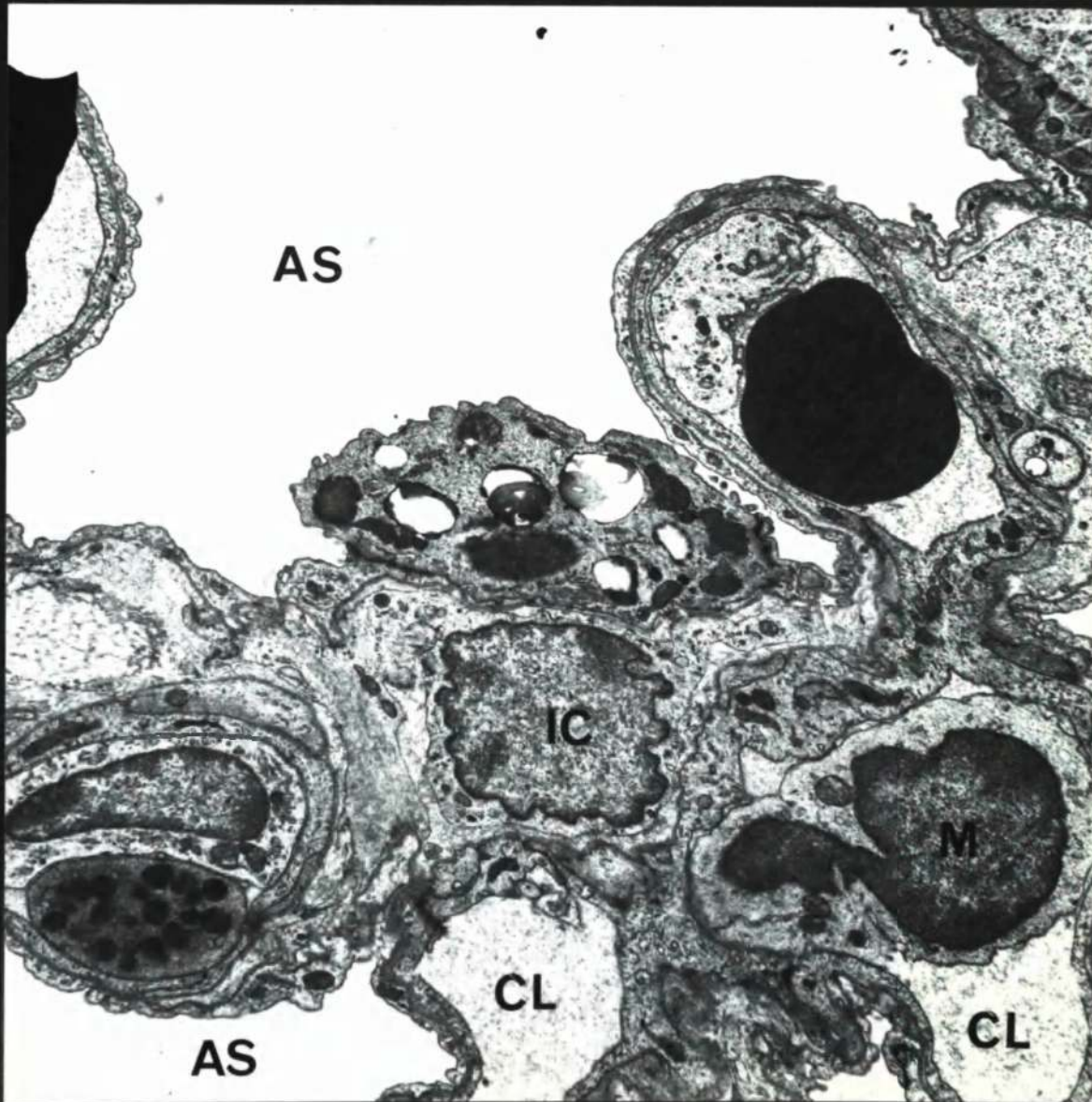


Fig. 129 Bovine lung: an alveolar wall separates two alveolar spaces (AS). An interstitial cell (IC) containing lysosomes lies beneath the basement membrane of the type 1 pneumonocyte (large arrow) and apparently outwith the basement membrane (small arrows) of the capillary endothelial cells (EC).

(OsO₄, x 10,000)

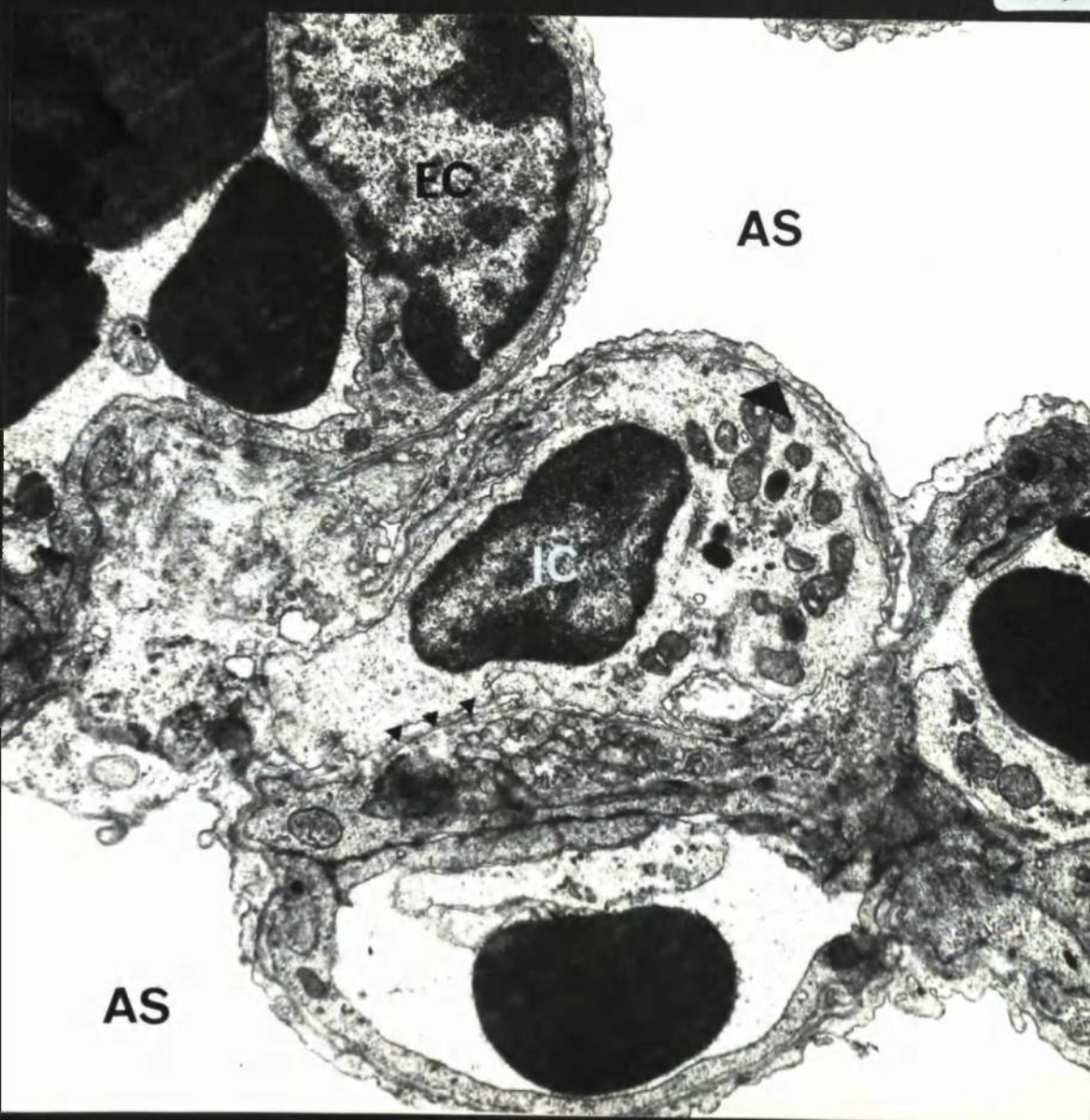


Fig. 130 Bovine lung: an interstitial cell (IC2) lies in the alveolar wall. The cell contains many largely empty vesicles and a few mitochondria. The alveolar space (AS) is indicated (left).

(OsO₄ x 10,000)

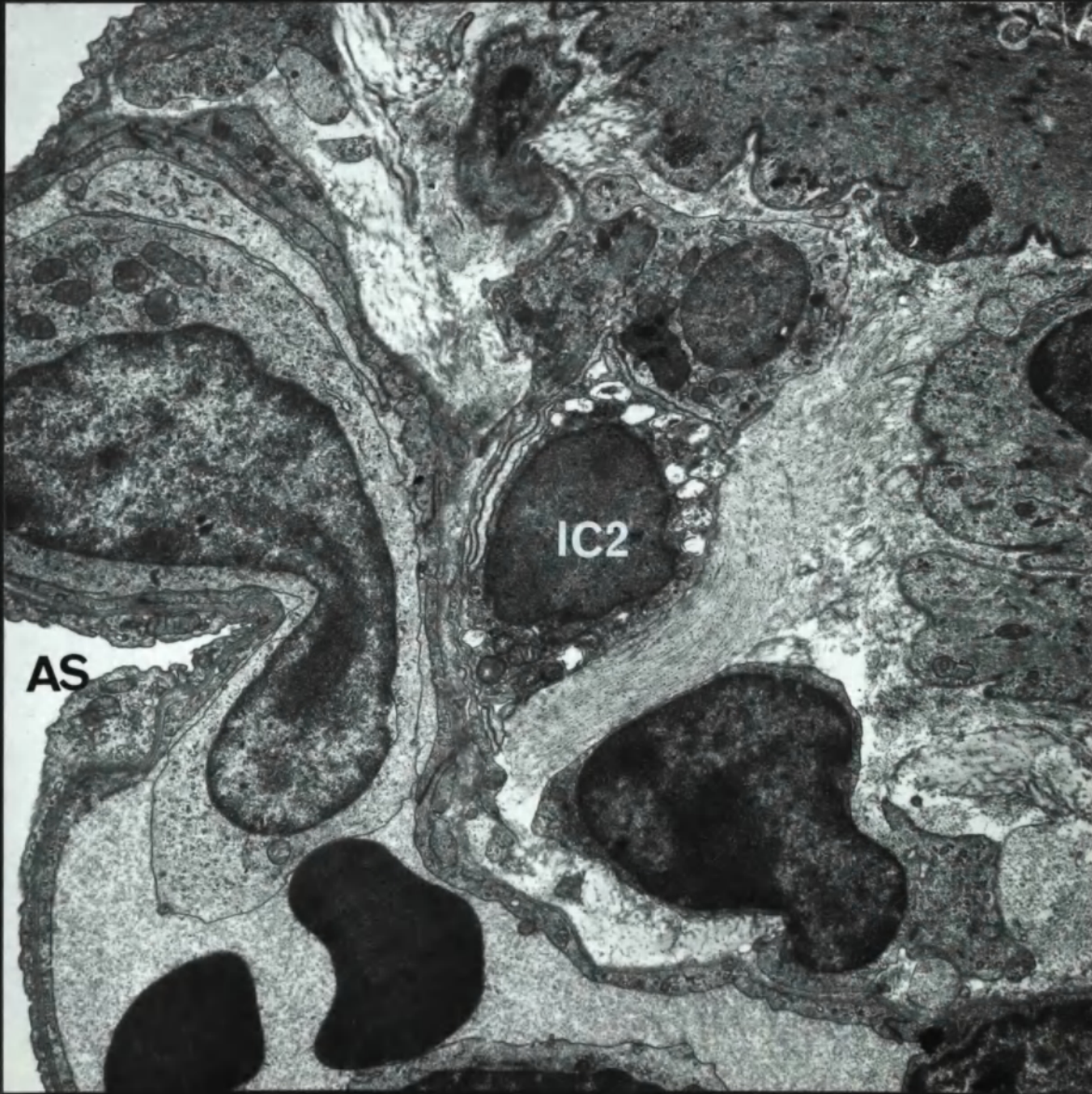


Fig. 131 Bovine lung: portion of alveolar duct. A capillary (top right) bulges into the alveolar space (AS). Cytoplasm of type 1 pneumonocytes (1) covers the surface of the alveolus, extending to the junction with another type 1 cell (top arrow); a further junction is apparent (left, double arrow). Elastic tissue (E), ground substance and a smooth muscle cell (S) lie in the interstitium.

(OsO₄, x 6000)

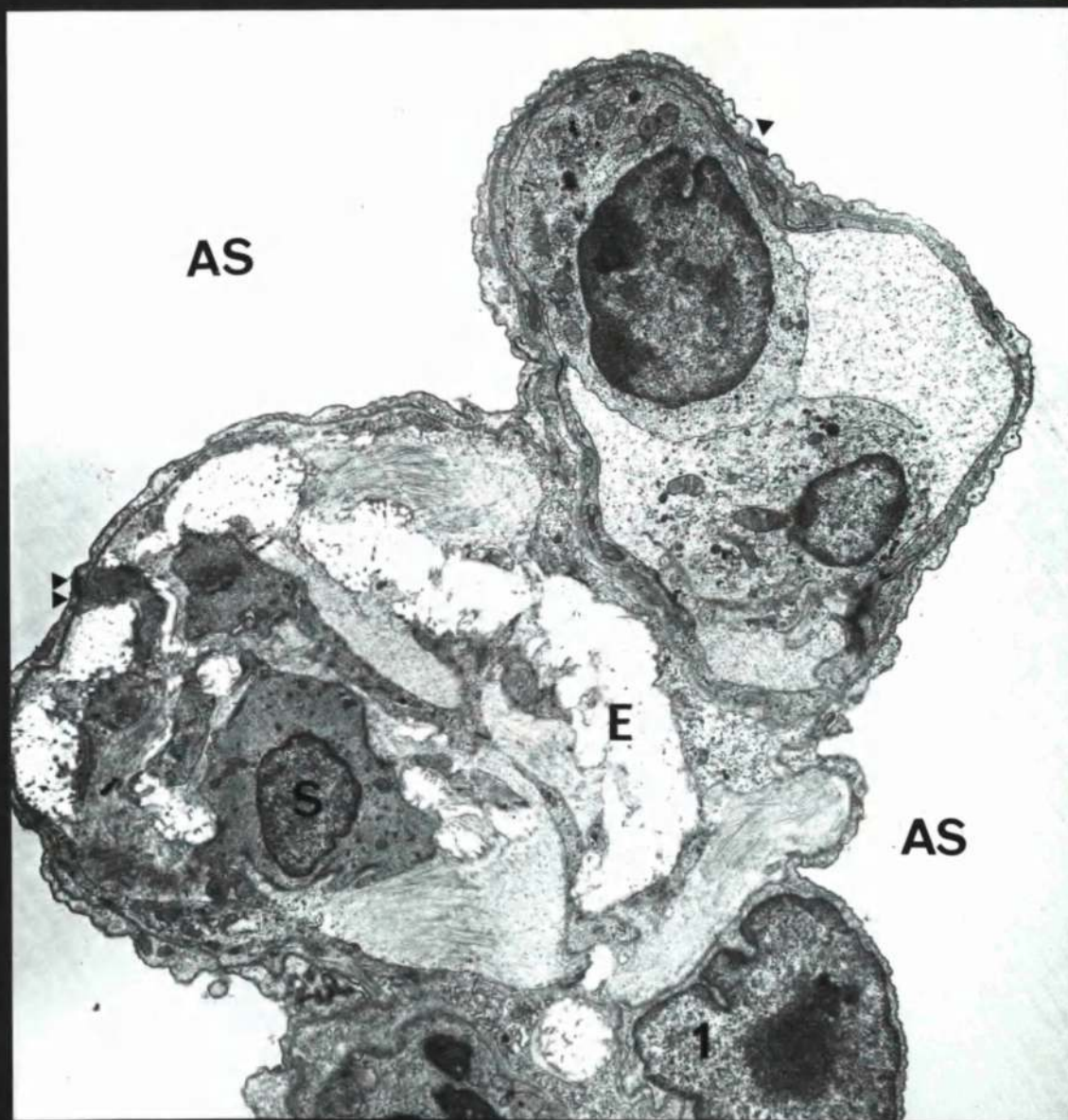


Fig. 132 Bovine lung: connective tissue in the alveolar septum between two alveolar spaces (AS). Collagen (C), elastin (E) and smooth muscle fibres (S) are apparent.

(OsO₄, x 6000)

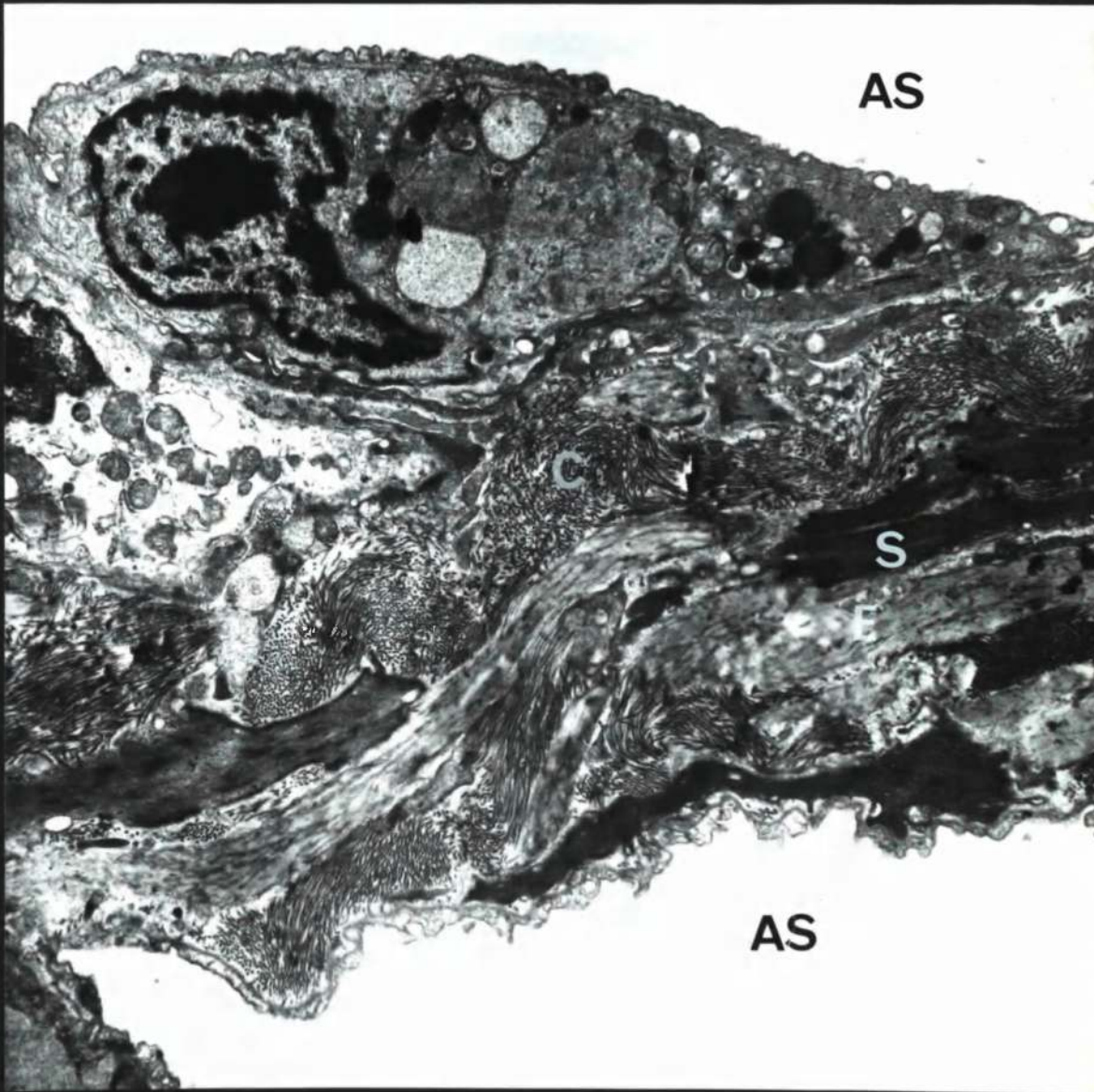


Fig. 133 Normal bovine lung: type 2 pneumonocytes (2) stain light reddish brown whereas alveolar macrophages (A) and cell in interstitium (I) stain bright red.

(AS-TR phosphate, x 1000)

Fig. 134 Normal bovine lung: type 2 pneumonocytes (2) stain light red-brown and cell in interstitium (I) stains bright red.

(AS-TR phosphate, x 1000)

Fig. 135 Normal bovine lung: cell in interstitium stains bright red and is possibly in a capillary.

(AS-TR phosphate, x 1000)

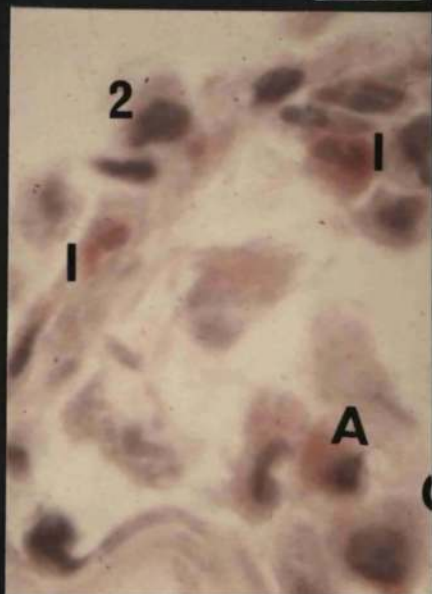
Fig. 136 Fog fever: hyperplastic alveolar epithelial cells do not stain but bright red cells are apparent in the interstitium of the alveolus and in the lumen.

(AS-TR phosphate, x 1000)

Fig. 137 Fog fever: some of the cells in the alveolar spaces stain bright red, cells in alveolar epithelium do not stain.

(AS-TR phosphate, x 250)

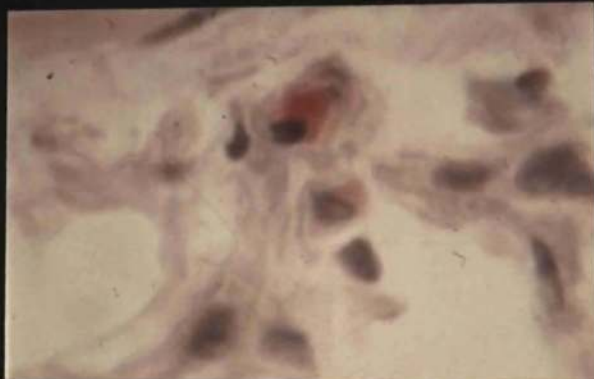
133



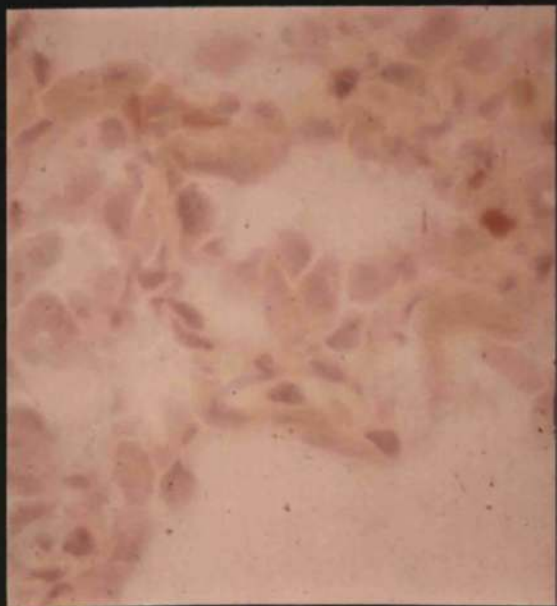
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135



136



137

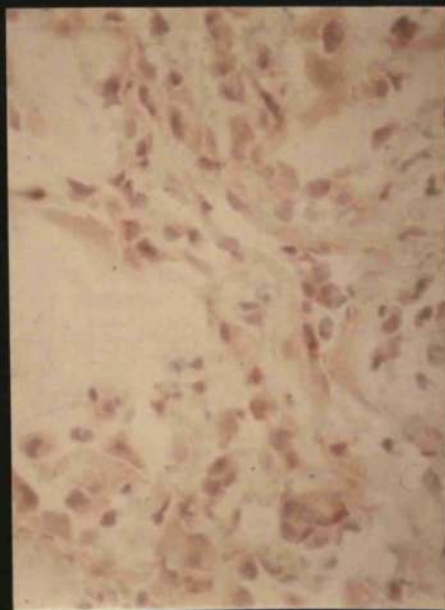


Fig. 138 Fog fever: alveolar space (AS) is lined by cuboidal cells (2) resembling type 2 pneumonocytes. These have surface microvilli, rest on a basement membrane (large arrows) and form junctional complexes (J) with adjacent cells. Basement membranes of epithelium and capillary endothelium (small arrows) border an oedematous interstitium, in which an interstitial cell (IC) is visible. A capillary endothelial cell (EC) is marked in the capillary (top left).

(OsO₄, x 6000)

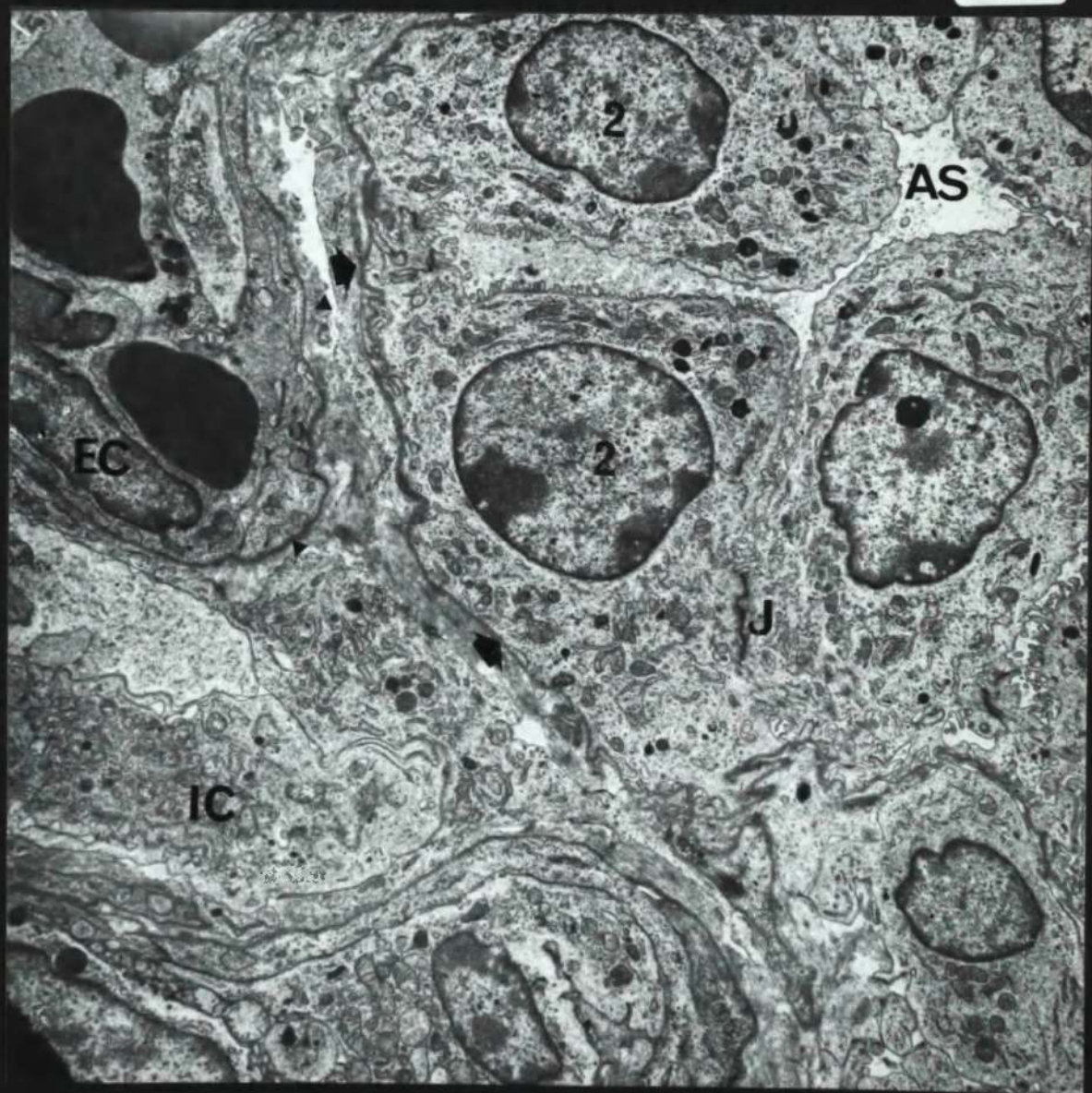


Fig. 139 Fog fever: alveolar epithelium. Type 2 pneumonocytes (2) project into the alveolar space (AS). Type 2 pneumonocytes have surface microvilli, dense, variably lamellated, inclusion bodies, a large Golgi apparatus and form functional complexes with adjacent cells (J). Basement membranes of epithelium (large arrow) and capillary endothelium (small arrows) are separated by oedematous connective tissue in which an interstitial cell is apparent (IC).

(OsO₄, x 10,000)

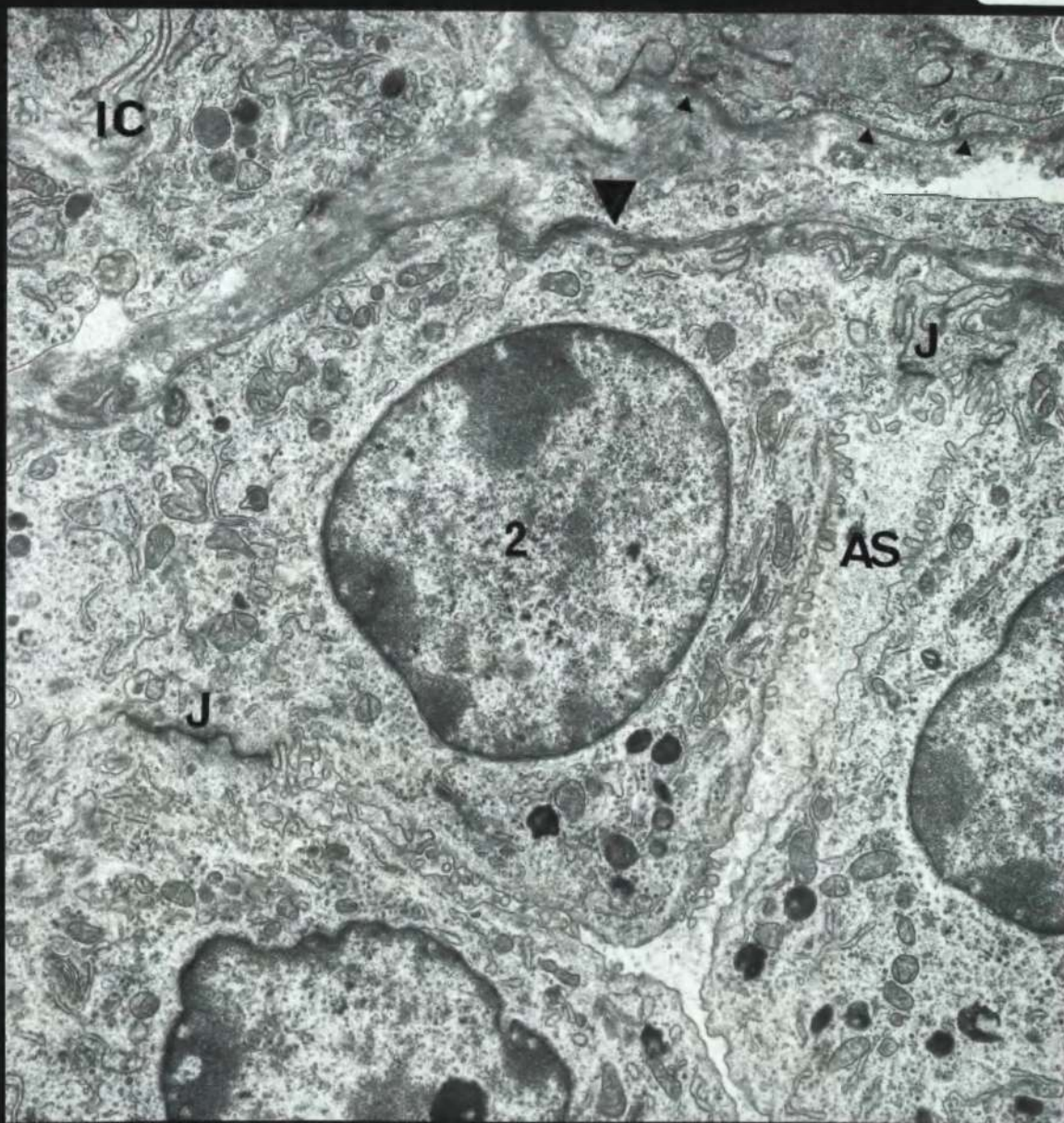


Fig. 140 Fog fever: type 2 pneumonocytes (2) project into the alveolar space (AS). The cells have surface microvilli, rest on a basement membrane (large arrows) and contain small, dense, sometimes lamellated inclusions. The Golgi apparatus (G) is large. The basement membrane of the capillary endothelium is indicated (small arrows).

(OsO₄, x 10,000)

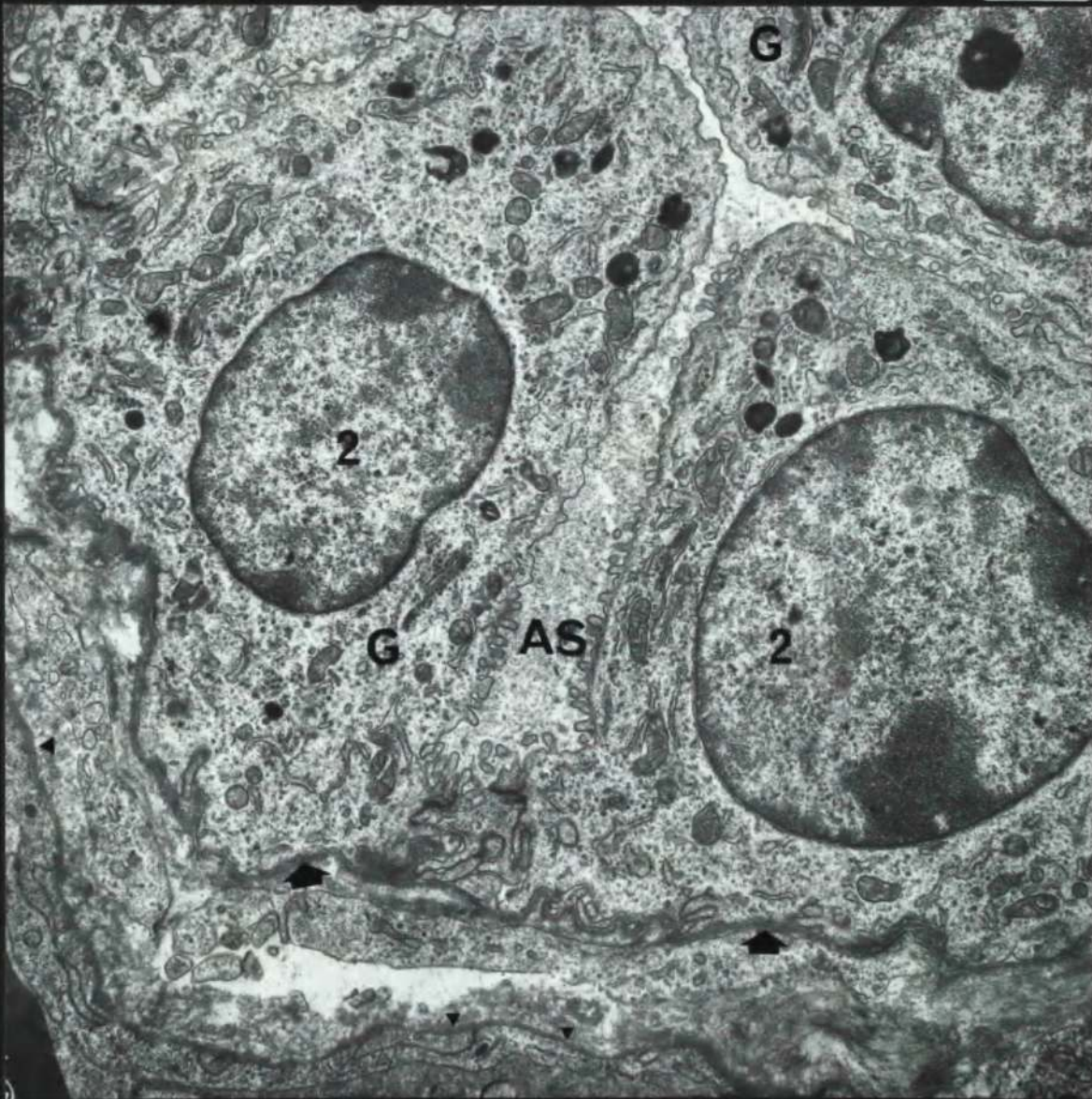


Fig. 141 Fog fever: early alveolar epithelial hyperplasia.

Type 2 pneumonocytes (2) separated by portion of type 1 pneumonocyte (1); many lamellated inclusions are visible in the type 2 pneumonocytes (top and bottom). The two alveolar spaces (AS) are separated by the alveolar wall, in which a capillary and a portion of an interstitial cell (IC) are apparent. Basement membranes of the epithelium (large arrows) and capillary endothelium (small arrows) are indicated. Both alveolar spaces are lined by type 2 pneumonocytes.

(OsC4, x 10,000)

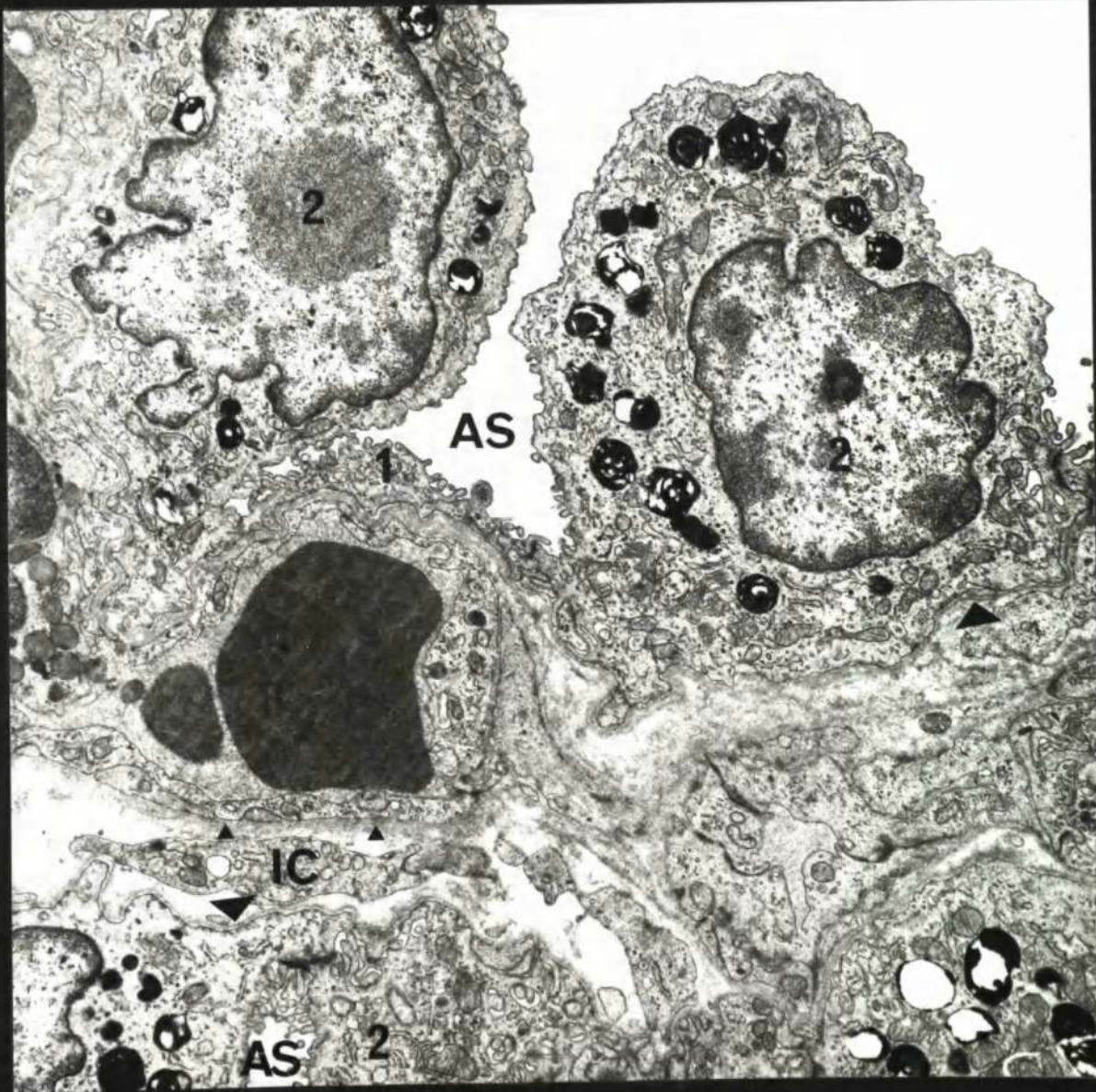


Fig. 142 Fog fever: type 2 pneumonocyte (2) of alveolar epithelium; note surface microvilli and abundant variably lamellated inclusions (IB). Cell junctions (laterally), many mitochondria and the Golgi apparatus are also visible. The alveolar space is marked (AS).

(OsO₄ x 20,000)

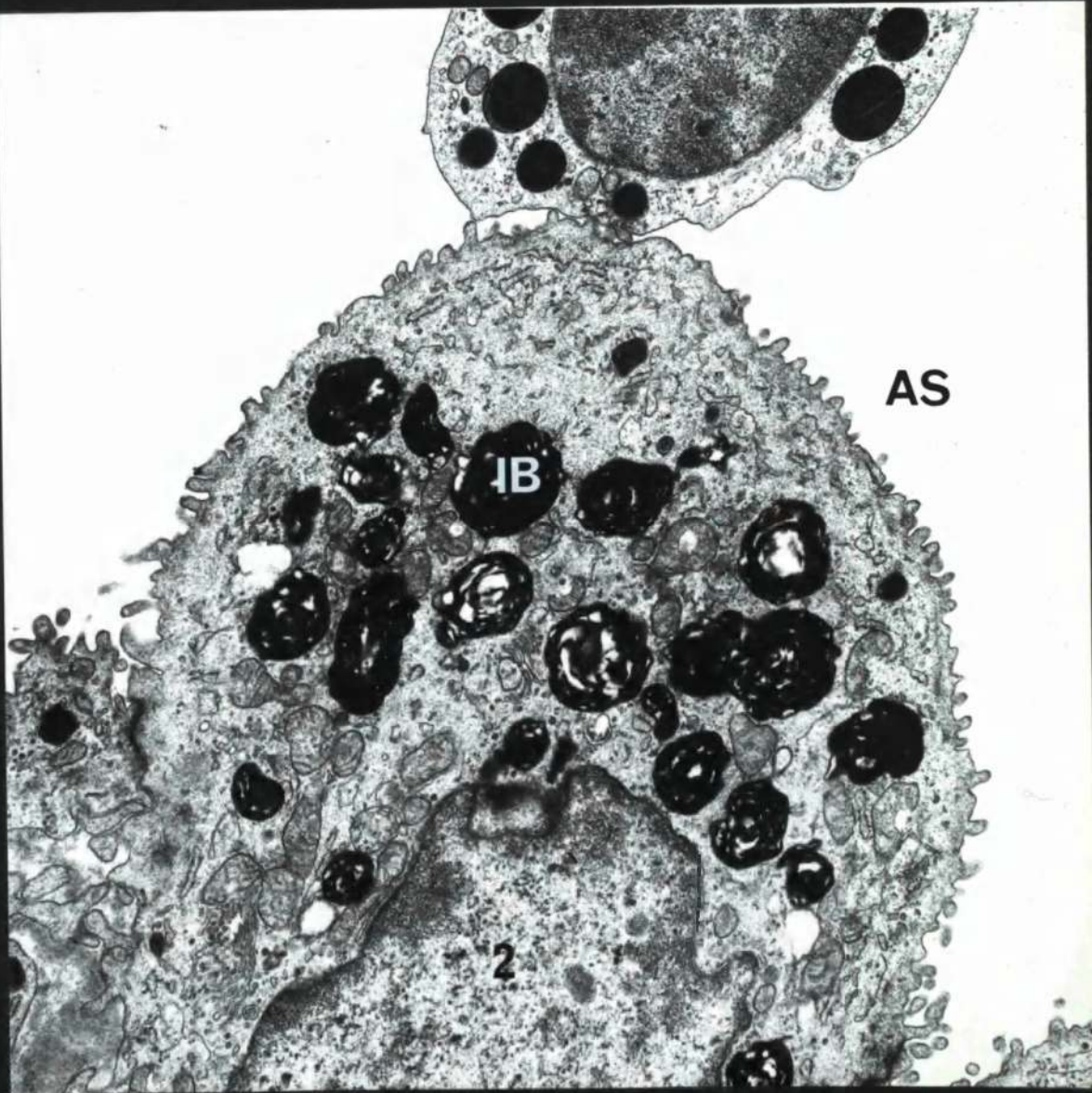


Fig. 143 For fever: alveolar epithelial hyperplasia.

Cuboidal type 2 pneumonocytes (2) are closely packed in the alveolar epithelium lining the alveolar space (AS). The basement membrane of the epithelium is marked (arrows). Junctional complex (J) and complex interdigitations of adjacent cells (top left) are apparent. Many variably electron dense, lamellated inclusions (IB) are present in the apical cytoplasm of type 2 pneumonocytes. A group of membrane bound vesicles (V) of unknown function are apparent in one cell.

(OsO₄, x 15,000)



Fig. 144 Fog fever: an alveolar macrophage (AM) in the alveolar space. Note long cytoplasmic projections (top left) Fine filament bundles near nucleus (F) and dense phagosome (lower left). Lamellated whorled, membrane like bodies (LB) lie free in the lumen.

(CsO₄† x 15,000)

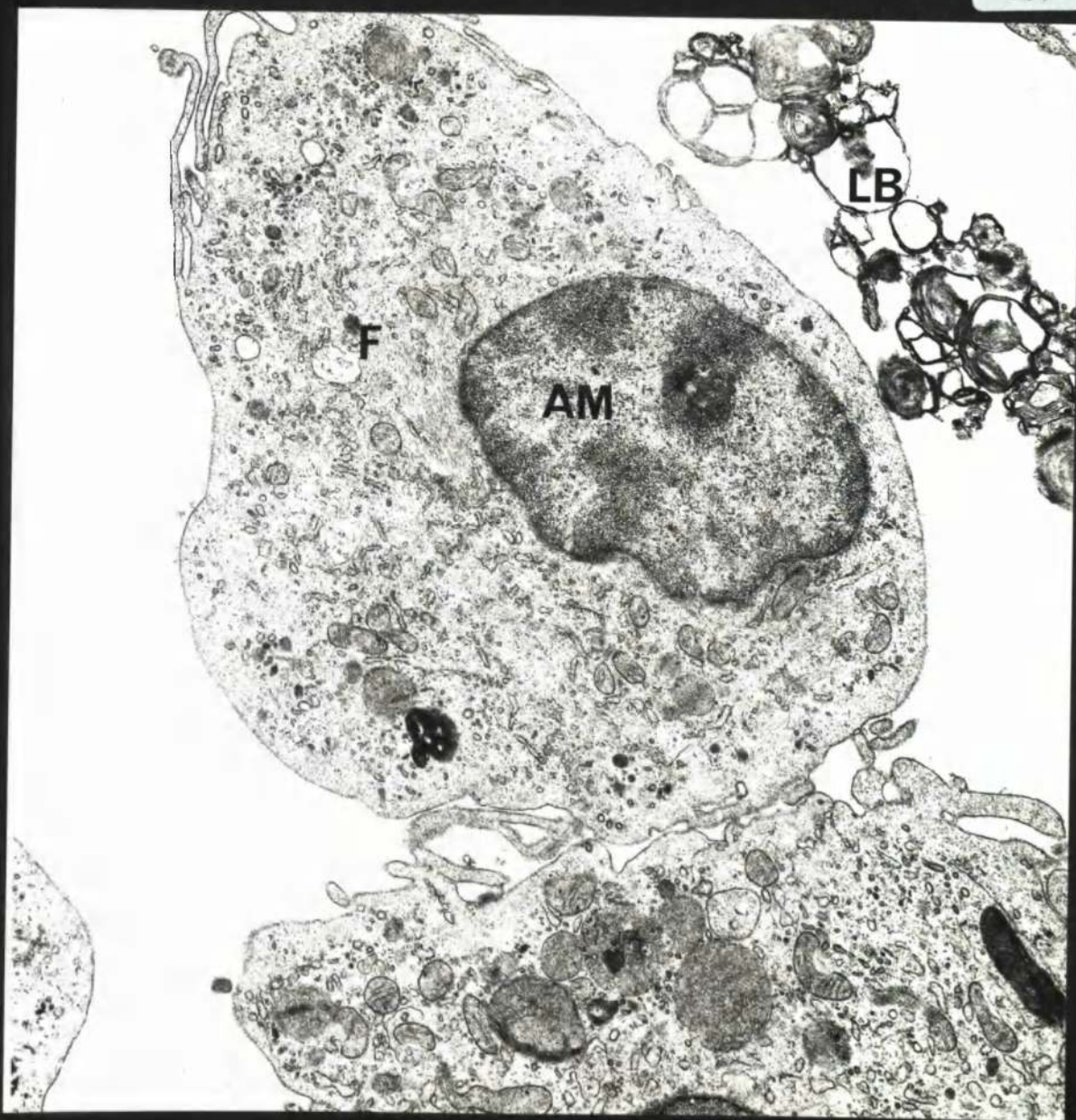
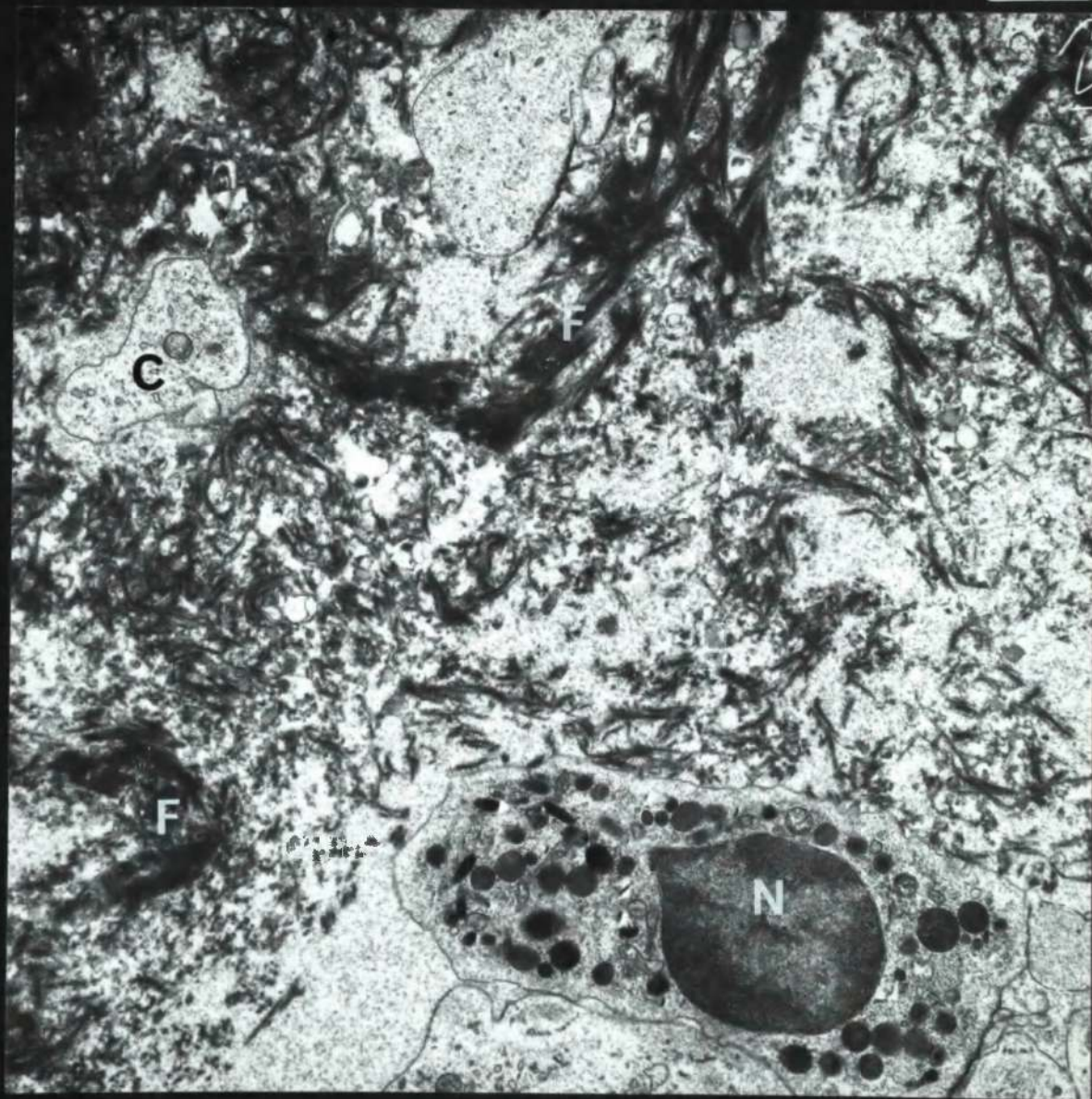


Fig. 145 Fog fever: the alveolar space contains a neutrophil (N), portions of effete cell cytoplasm (C) and fibrillar material resembling fibrin (F).

(OsO₄, x 10,000)



FIGURES FOR MACROSCOPIC AND HISTOPATHOLOGICAL LESIONS: EXPERIMENTS

Fig. 148 Subpleural and interstitial emphysema in ventral
parts of cardiac and diaphragmatic lobes.

Fig. 149 Detail of Fig. 148.

148



149

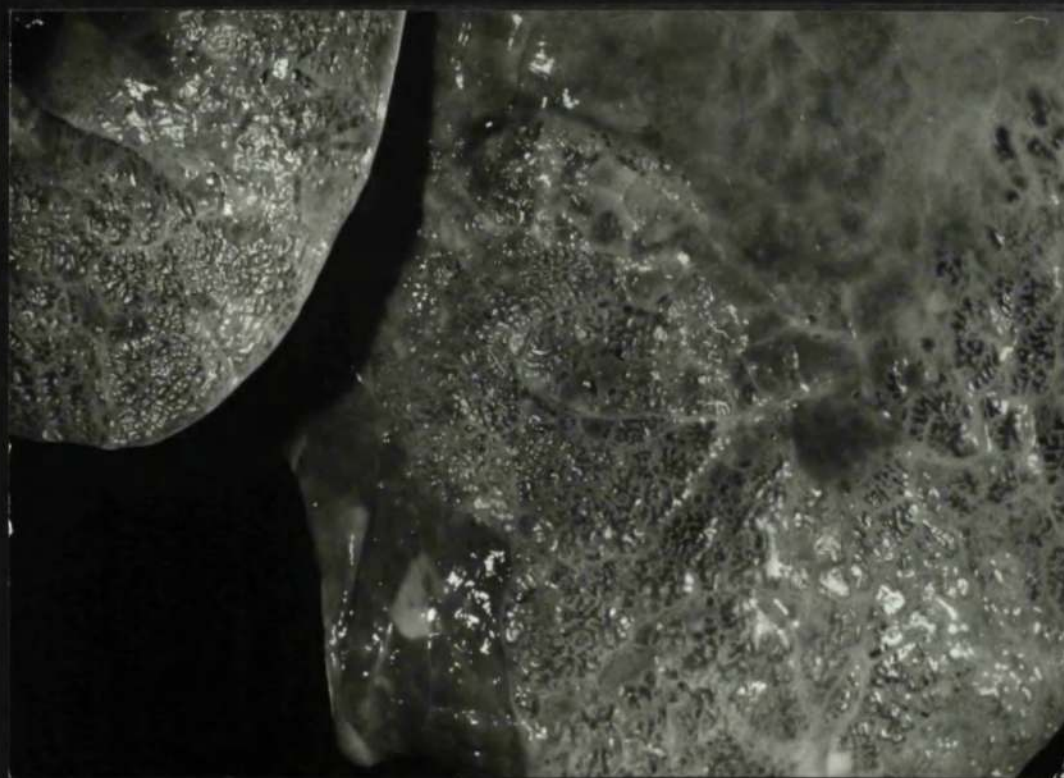


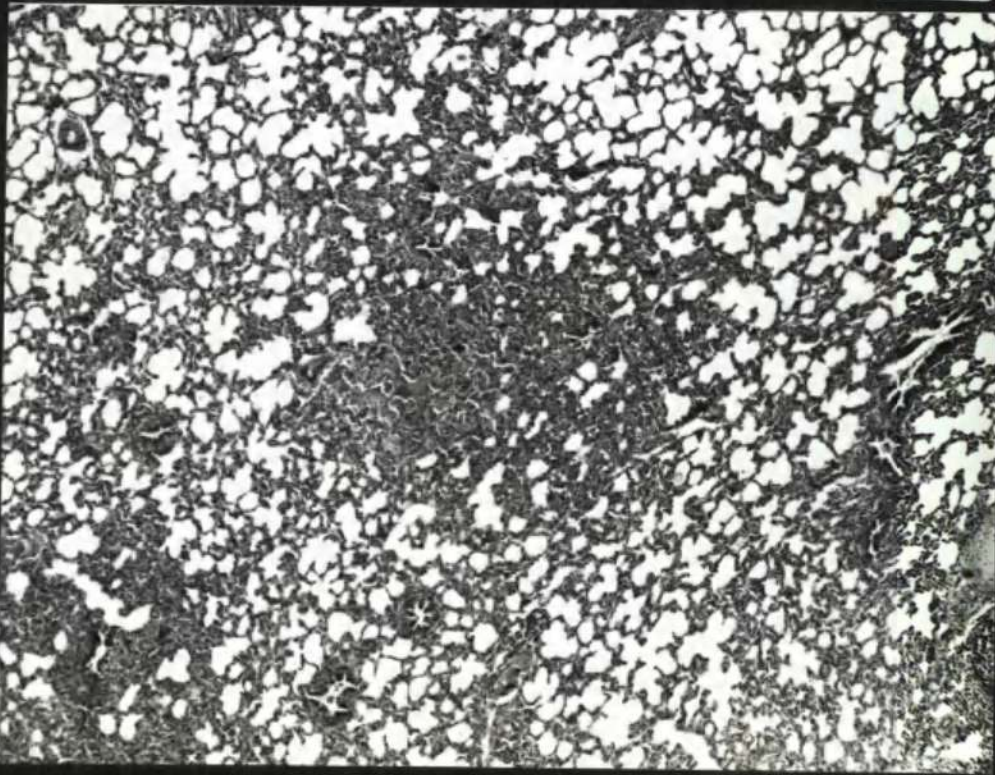
Fig. 150 focal lesion in centre of lobule

(H+E, x 50)

Fig. 151 Detail of Fig. (150). Oedema and hyaline membranes
in alveolar spaces and proliferation of alveolar
epithelial cells.

(H+E, x 300)

150



151

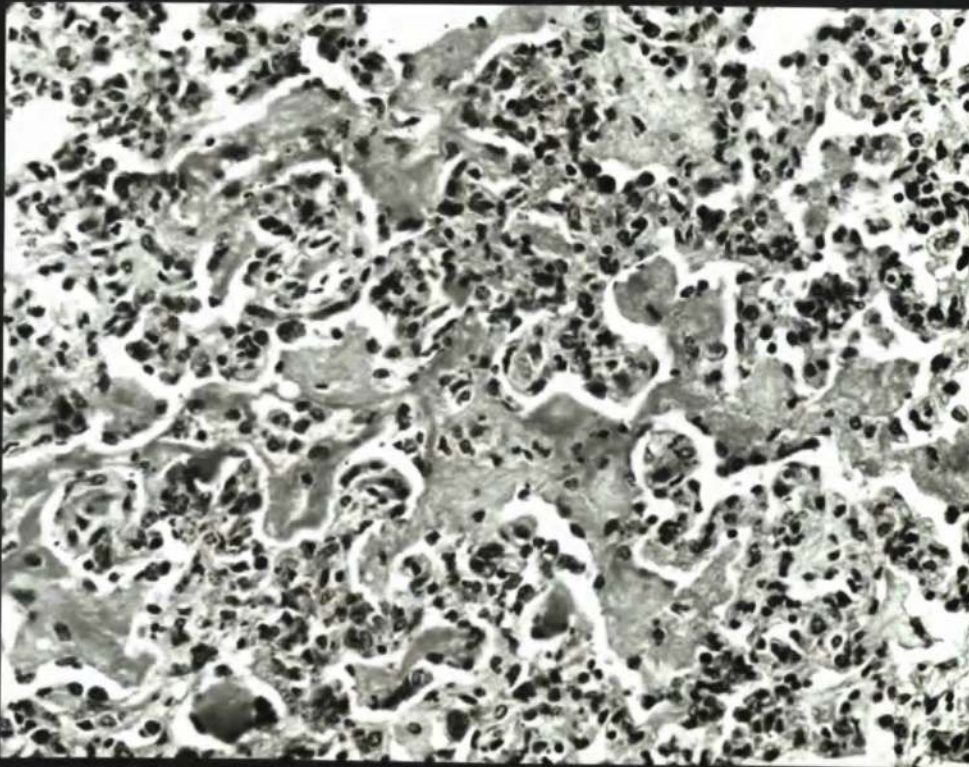


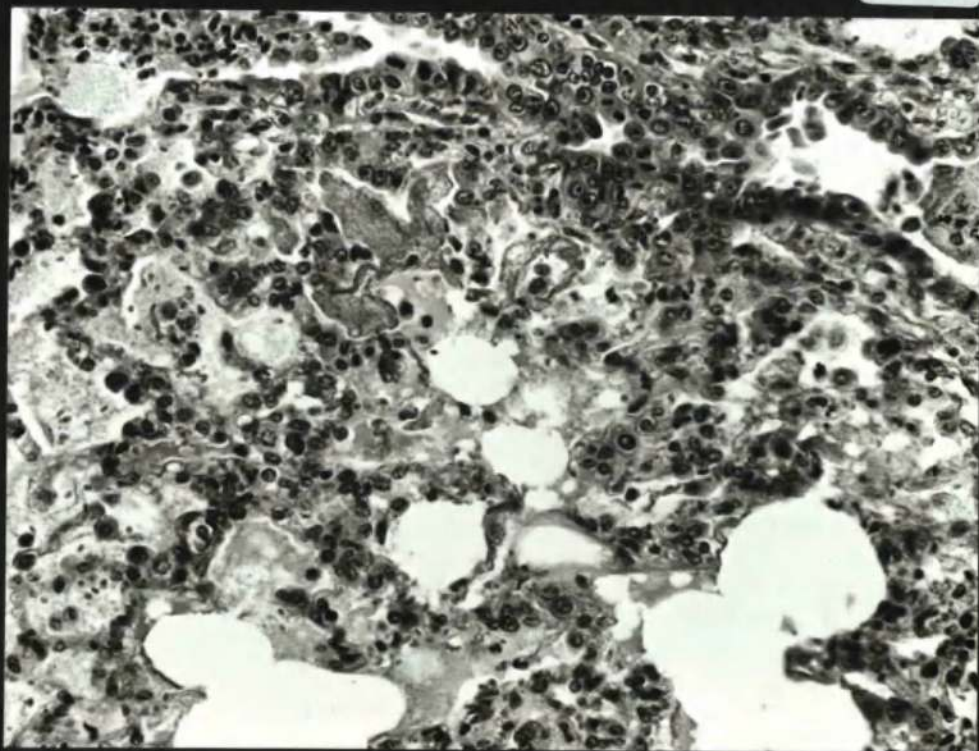
Fig. 152 Mitotic figures in bronchiolar epithelium with pulmonary oedema, hyaline membranes and proliferation of alveolar epithelial cells.

(H+E, x 300)

Fig. 153 Proliferation of alveolar epithelial cells and accumulation of large mononuclear cells in alveolar spaces.

(H+E, x 300)

152



153

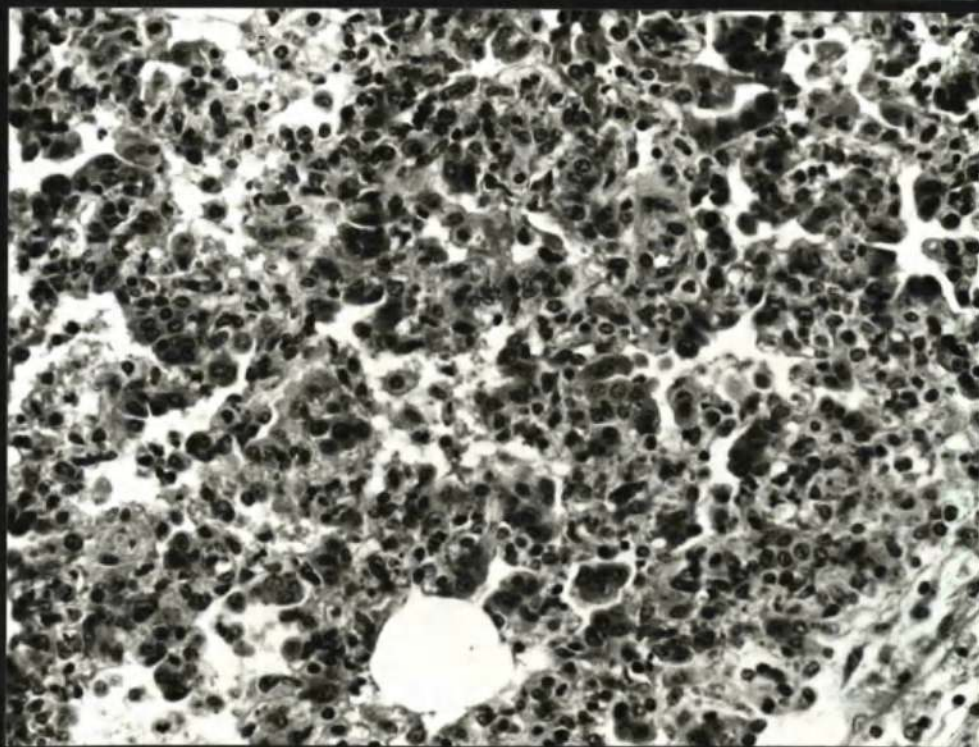


Fig. 154 Overinflation and focal lesion of one lobule with
widespread alveolar epithelial hyperplasia in
lower lobule.

(H+E, x 50)

Fig. 155 Large mononuclear cells in alveolar spaces and
alveolar epithelial hyperplasia in part of the
lung lobule.

(H+E, x 50)

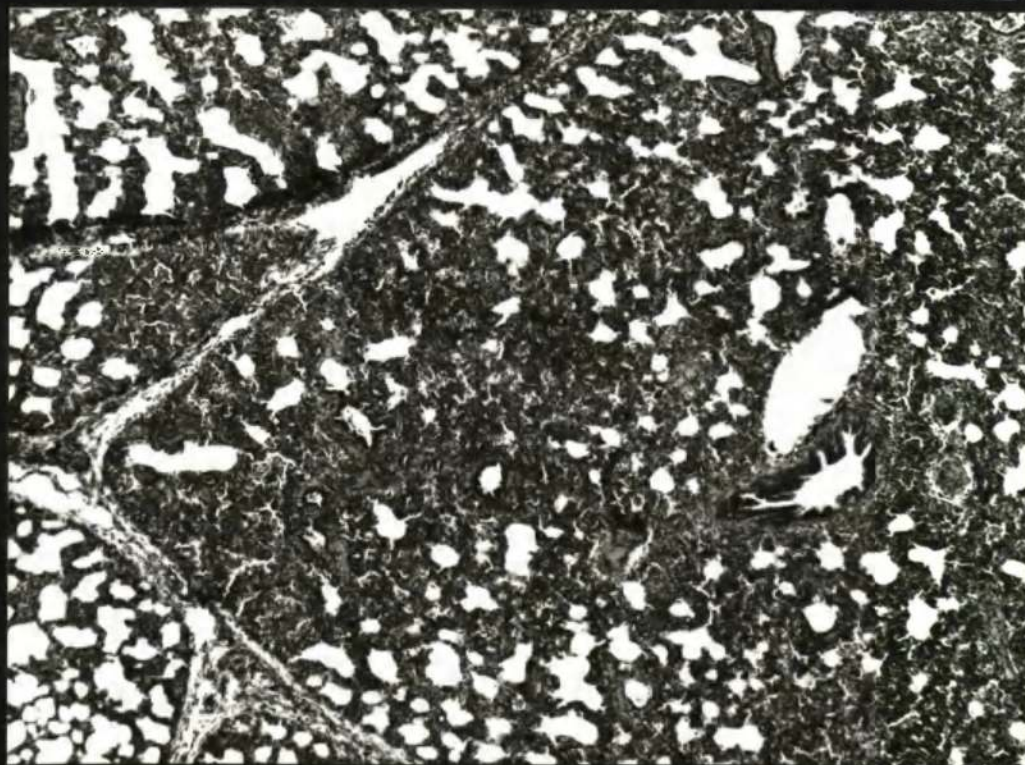


Fig. 158 Lungs of calf (J) four days after administration of Bordetella pertussis suspension, note diffuse colour change resulting from alveolar epithelial hyperplasia.

Fig. 159 Lungs of calf (J) four days after administration of Bordetella pertussis suspension; diffuse colour change involves all lung substance and is the result of alveolar epithelial hyperplasia.

158



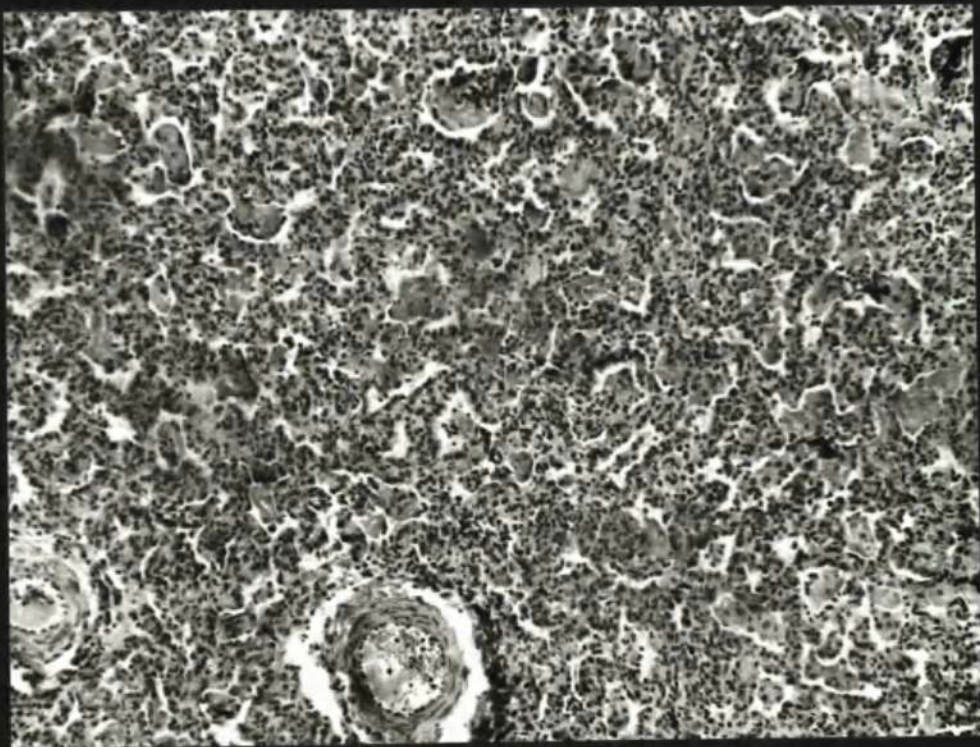
159



Fig. 160 Diffuse alveolar epithelial hyperplasia with accumulation of large mononuclear cells, hyaline membranes and oedema fluid in alveolar spaces of calf (J). The alveolar septa are dilated by oedema.
(H+E, x 110)

Fig. 161 Apical lobe from calf (J) with focus of cuffing pneumonia and overinflation or alveolar epithelial hyperplasia of acini.
(H+E, x 50)

160



161

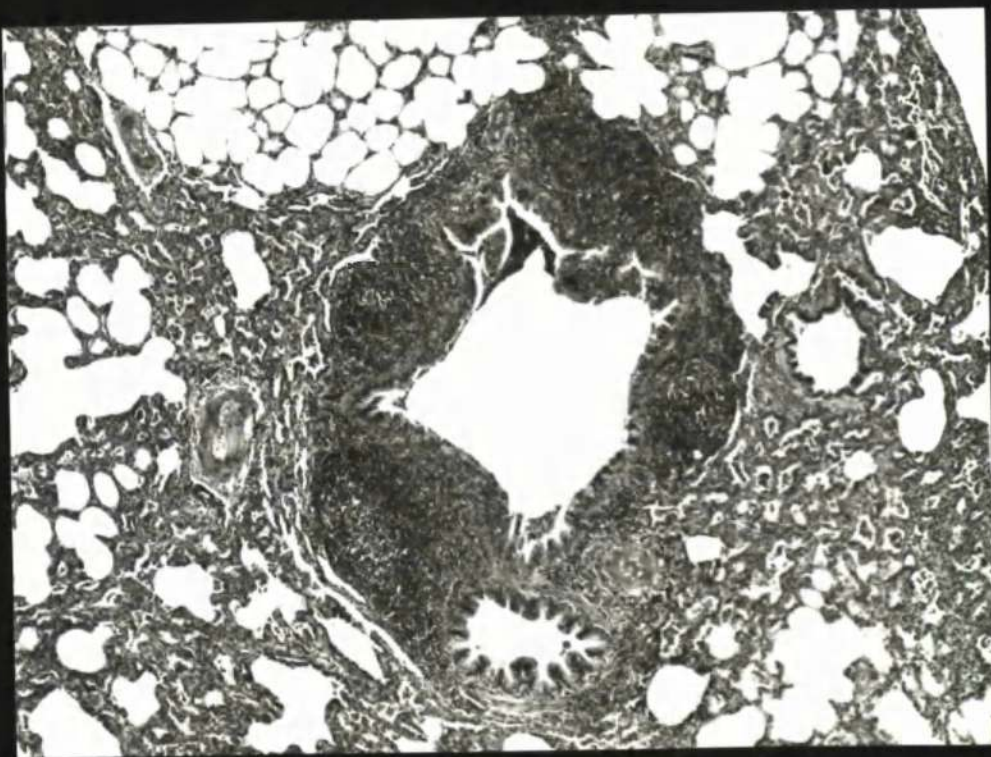


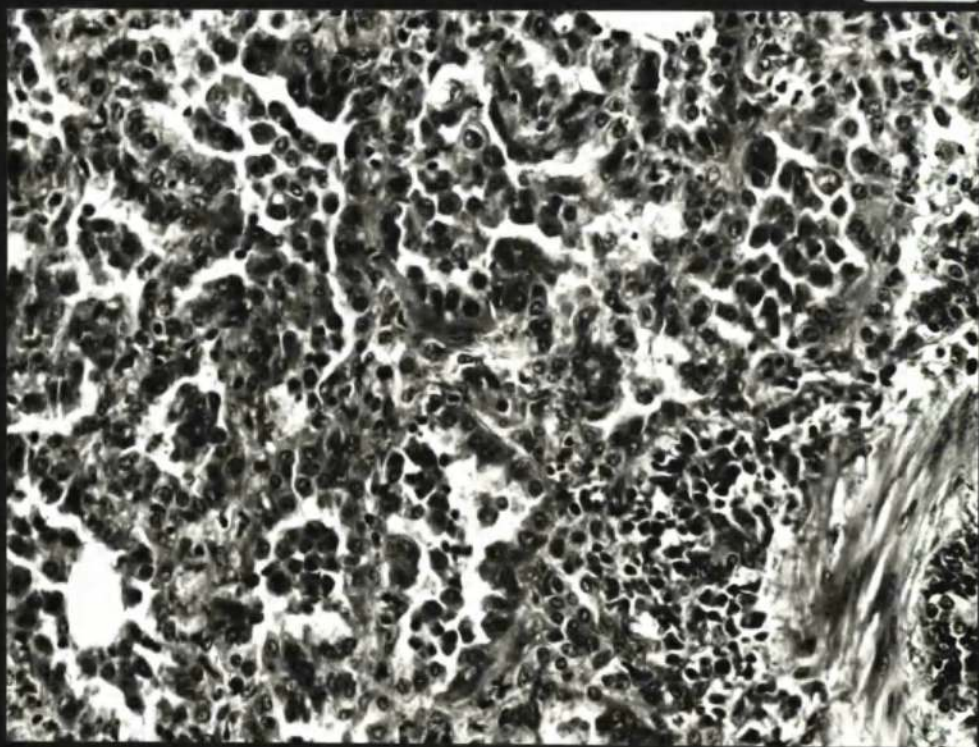
Fig. 162 Large mononuclear cells in alveolar spaces,
extensive alveolar epithelial hyperplasia and
oedema of alveolar septa in lung of calf (J).

(H+E, x 300)

Fig. 163 Hyaline membranes infiltrated by macrophages in
alveolar spaces and alveolar epithelial hyperplasia
in lung of calf (J).

(H+E, x 500)

162



163

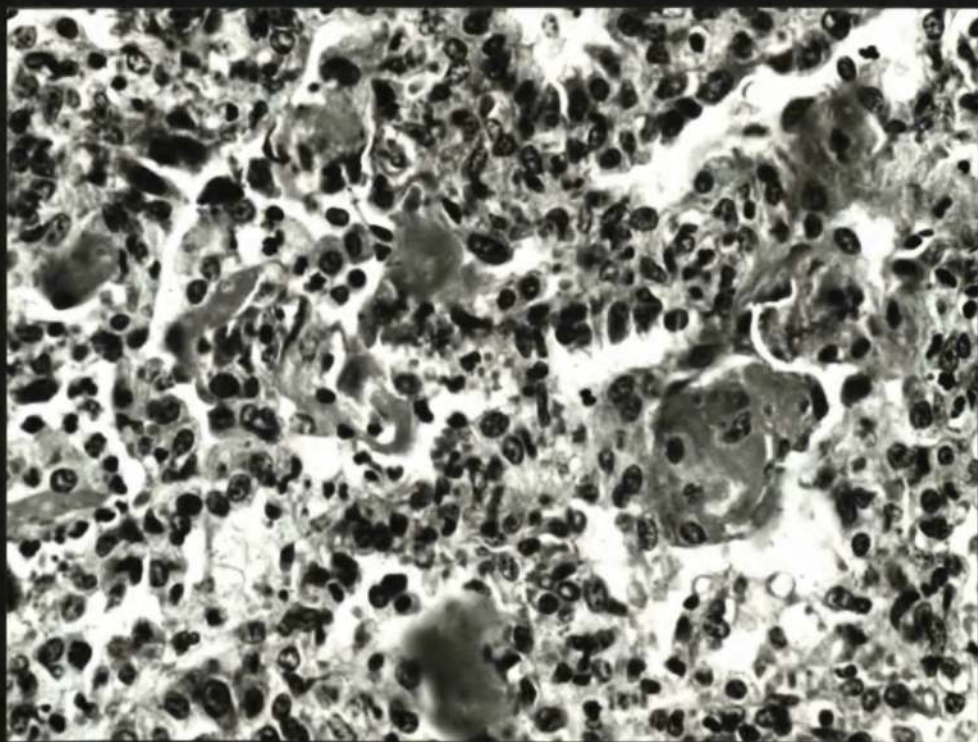


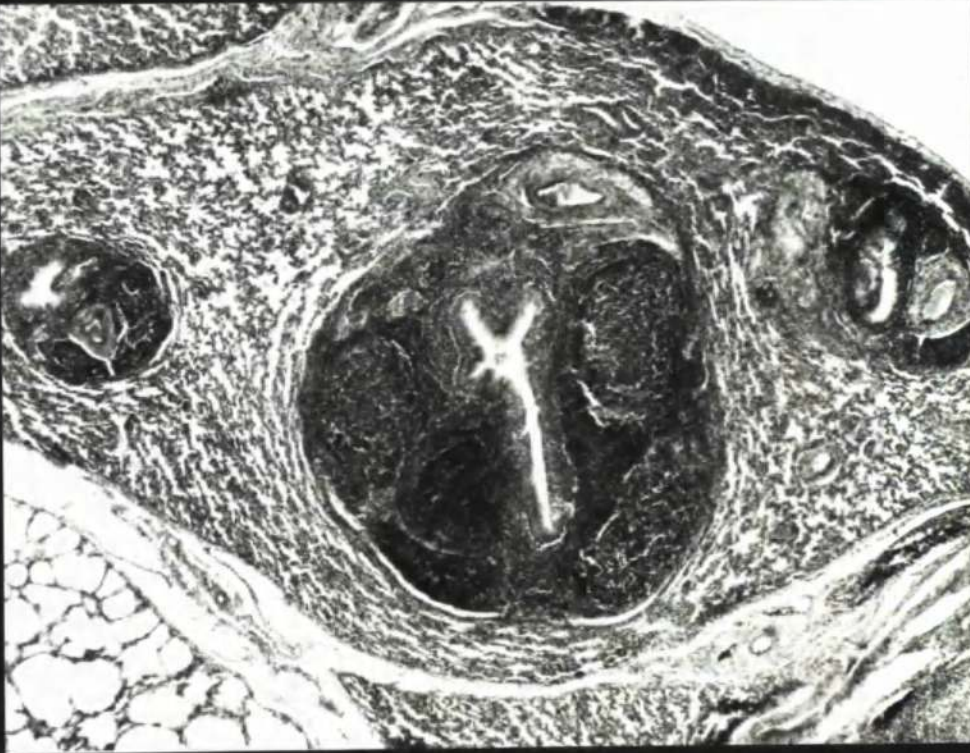
Fig. 164 Cuffing pneumonia with collapse.

(H+E, x 50)

Fig. 165 Severe cuffing pneumonia.

(H+E, x 50)

164



165

